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ELECTROCARDIOGRAPHIC STUDIES IN PULMONARY DISEASE.

III. DETECTION OF DIFFUSE LUNG DISEASE FROM THE NORMAL ELECTROCARDIOGRAM: CORRELATION WITH PULMONARY FUNCTION STUDIES AND CLINICAL AND ROENTGEN FINDINGS

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Diffuse lung disease has distinctive effects upon the electrocardiogram (1). These are sufficiently characteristic to permit detection of lung disease from the electrocardiogram with an over-all accuracy approaching 90 per cent (2). The impetus for these investigations was the work of Zuckermann and associates (3) who first called attention to the more subtle effects of lung disease on the atrial complexes. Prior to their studies, the P-pulmonale of Winternitz (4) and the vertical tendency of the QRS axis in some cases of lung disease were well known. P-pulmonale is present in relatively few cases, but is highly specific; a vertical QRS axis (*i.e.*, to the right of +60°) is found in approximately half the cases, but is nonspecific (1).

The key electrocardiographic abnormality of lung disease is verticalization of the mean P-wave axis. In conjunction with characteristic modifications of P-wave morphology, this has provided some accurate criteria for the electrocardiographic detection of diffuse lung disease (2) (Fig. 1). There is one group of patients in whom the diagnosis of lung disease is suggested by the electrocardiogram alone, although the tracings are normal by the usual electrocardiographic standards. Heart disease is not implied by such findings; nevertheless, these diagnostic features of the electrocardiogram may be abnormal and due (at least in part) to extracardiac factors.

MATERIAL AND METHODS

Tracings were reviewed in 200 consecutive cases in which the presence of lung disease could be inferred from the electrocardiogram (ECG). In every instance the tracing was read without any knowledge of the patient and the interpretation was confirmed by comparison with clinical, roentgen and pulmonary function data.

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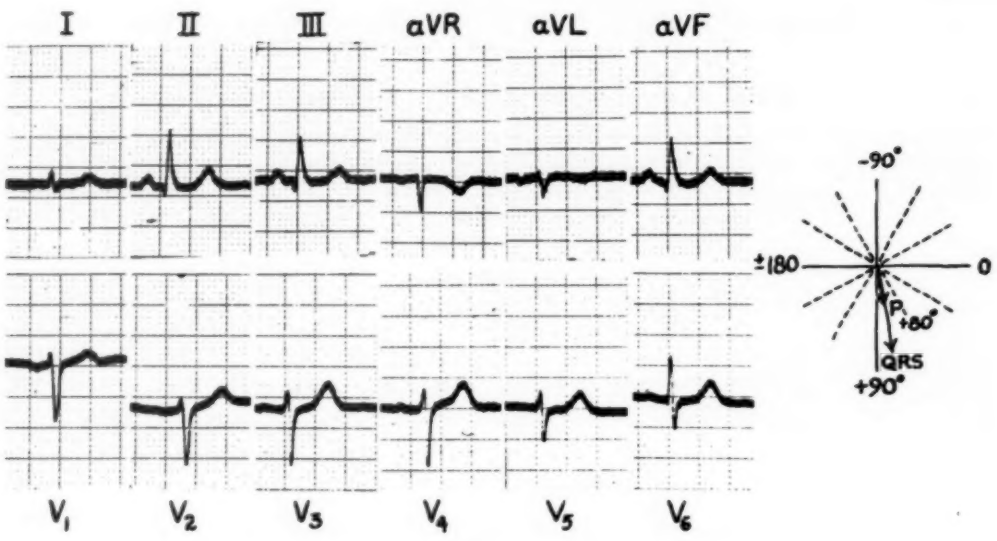

FIG. 1. (Patient #35, a 57-year-old man with pulmonary emphysema.) "Normal" tracing demonstrating the principal electrocardiographic criteria for the diagnosis of diffuse lung disease. P axis = +80°; QRS axis = +80°. Gothic P wave in leads II, III and aVF. Diphasic (+−) P wave in leads V_1 and V_2. S wave over 2 mm. to position V_6.

Thirty-seven patients had tracings "diagnostic" of lung disease, yet normal by standard electrocardiographic criteria. These are the subject of this report. Chest roentgenograms were obtained in every case. Pulmonary function tests were performed in 29 of the 37.

The following three criteria, previously established in Part II of these studies (2), were employed for the interpretation "consistent with diffuse lung disease"[1]:

1. P-pulmonale[2] or unmistakable Gothic[2] P wave in leads II, III and aVF (Figs. 1–4).
2. P wave axis[2] = +70° or more, plus either or both of the following:
   (a) Diphasic (+−) P waves in precordial leads, at least to position V_2.
   (b) S wave = 2 mm. or more in precordial leads, at least to position V_5.
3. P wave axis = +60°, plus both 2(a) and 2(b), plus vertical or "axis-illusion" QRS axis[2].

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[1] Two other patients with lung disease and "normal" electrocardiograms demonstrated the criteria for the interpretation "possibly consistent with diffuse lung disease" (2).

[2] *P-pulmonale:* (This finding when associated with right atrial enlargement, excluded patients from the present study.) Single-peaked P waves of normal duration in leads II, III and aVF, but = 0.26 millivolt or greater in amplitude in any one or all of these leads.

Gothic P-wave (Zuckermann *et al.* (3)): Definite single-peaking of P waves of normal dimensions (maximum: 0.1 second × 0.25 millivolt) in leads II, III and aVF (Figs. 1–4).

P-wave axis: The mean manifest vector of the P waves derived from the frontal plane (limb) leads and numerically oriented according to the standard hexaxial modification of the Bayley reference system. For practical purposes, clear P-wave negativity in lead aVL defines a P-axis greater than +60° (*i.e.*, a vertical P-axis).

"Axis illusion" QRS: A QRS axis either "indeterminate" (equally positive and negative or flat QRS in all limb leads) or extremely "leftward" oriented (−80° or −90°) with deep S waves across the precordium. Such axes are the equivalents—in space—of a manifestly vertical QRS axis.

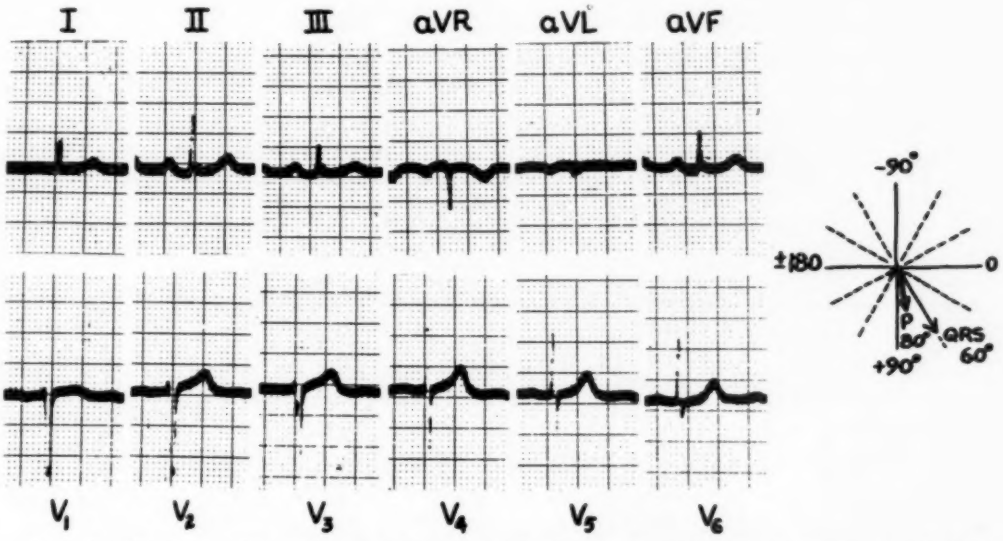

FIG. 2. (Patient #25, a 66-year-old man with chronic bronchitis, emphysema and right heart failure (cor pulmonale)). Electrocardiogram completely within normal limits except for evidence of diffuse lung disease. P axis = +80°; QRS axis = +60°. Gothic P wave in leads II, III and aVF. Diphasic P wave in Leads V_1 and V_2. S wave over 2 mm. to position V_6. QRS axis intermediate. Cardiac electrical position semivertical.

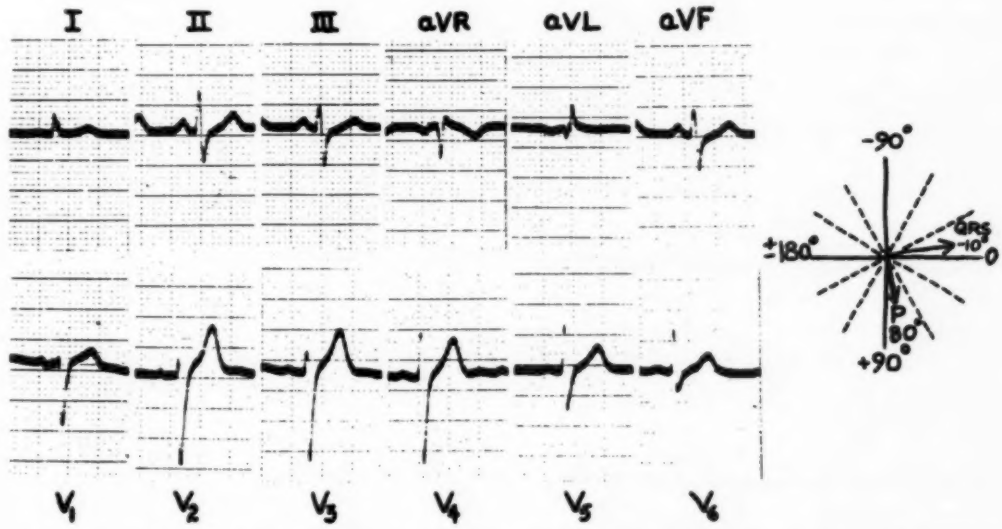

FIG. 3. (Patient #32, a 45-year-old man with asthma and pulmonary emphysema.) Electrocardiogram within normal limits except for evidence of diffuse lung disease. P axis = +80°; QRS axis = −10°. Gothic P wave in leads II, III and aVF. S wave over 2 mm. to lead V_6. QRS axis horizontal. Cardiac electrical position semivertical.

RESULTS

Figures 1 to 5 illustrate several varieties of tracings which, although unequivocally diagnostic of lung disease, could be considered within normal limits by standard electrocardiographic criteria.

Table 1 summarizes the electrocardiographic, clinical and roentgen data in these cases. Every patient had clinically apparent lung disease. Two (Nos. 10 and 25) manifested clinical evidence of cor pulmonale. Of the 29 patients who underwent pulmonary function tests, all but one (No. 30) showed mild to marked

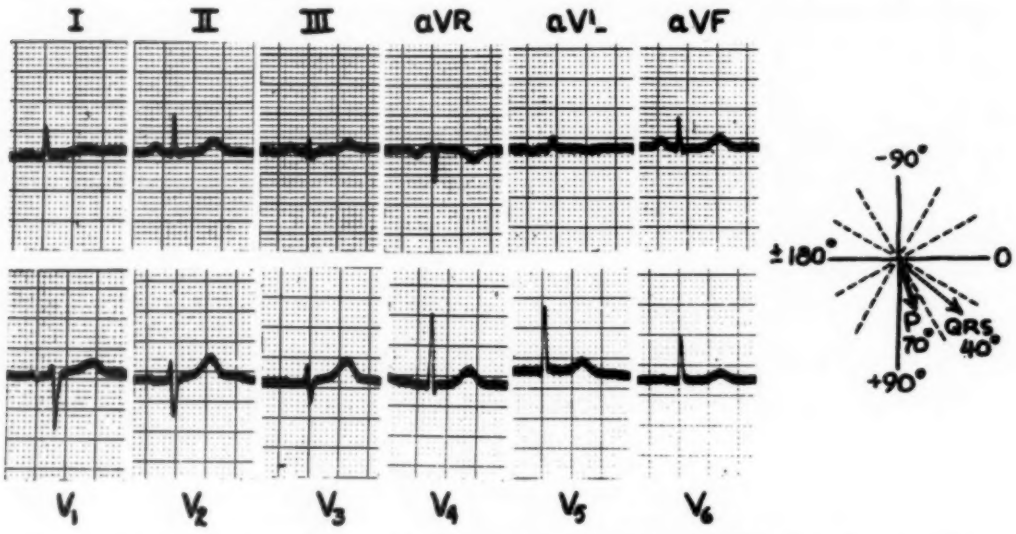

FIG. 4. (Patient #7, a 66-year-old man with emphysema and Whipple's disease.) Electrocardiogram within normal limits except for evidence of diffuse lung disease. P axis = +70°; QRS axis = +40°. Gothic P wave in leads II, III and aVF. Diphasic P waves in leads V_1 to V_3. The QRS axis intermediate. Cardiac electrical position semivertical.

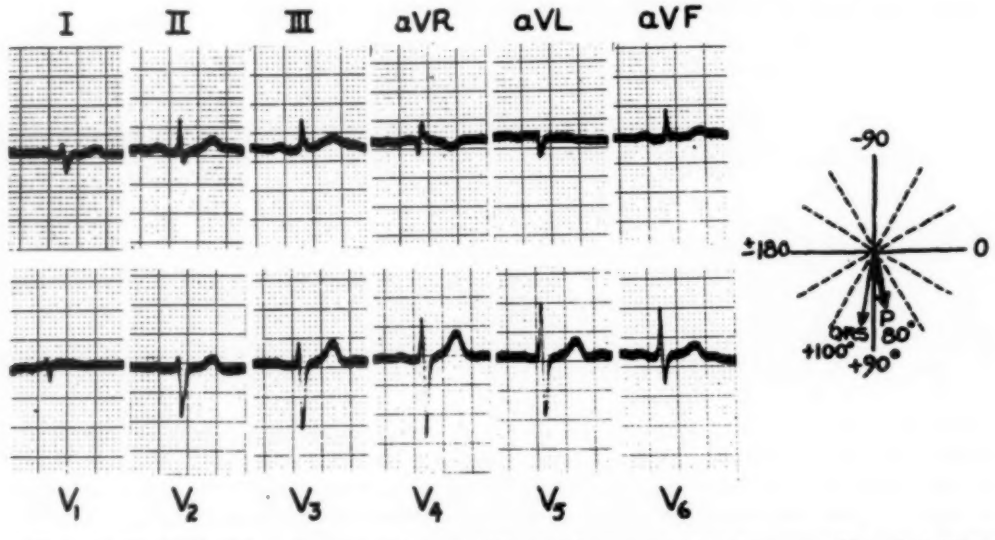

FIG. 5. (Patient #4, a 41-year-old man with emphysema and pulmonary fibrosis.) Electrocardiogram within normal limits except for evidence of diffuse lung disease. Right axis "deviation" (QRS axis = +100°), but no voltage or ST-T abnormalities indicative of right ventricular abnormality. In chest roentgenograms, the heart was normal. P waves of normal configuration, but P axis = +80°. Diphasic P waves in V_1 and V_2. S wave over 2 mm. to V_6.

respiratory impairment. Roentgenograms of the lungs were abnormal in every case. Thirty patients had normal cardiac silhouettes; 3 had questionable, and 2 had definite right ventricular enlargement; 2 others had left ventricular enlargement. In 27 patients (73 per cent of this series) the ECG demonstrated Gothic P waves; in 23, diphasic P waves in the precordial leads; and in 15, both phenomena. P wave axes were all between +70° and +90°, whereas QRS axes varied widely (−30° to +100°) (Figs. 3 and 4). In only 6 patients did the ECG demonstrate QRS axes of +90° to +100° (Fig. 5). Although these 6 cases might be considered examples of right axis "deviation," not one showed ST-T or voltage signs of right ventricular abnormality, and all had normal cardiac silhouettes.

DISCUSSION

It is not difficult to infer lung disease in patients whose electrocardiograms show classic P-pulmonale with or without electrical signs of right ventricular abnormality. When the changes are less gross, however, the diagnostic sensitivity of the electrocardiogram is put to the test. Our studies indicate that clear evidence of structural atrial or ventricular changes is not necessary for diagnosis. In none of the patients under consideration did the ECG show voltage, conduction or T-wave abnormalities, yet in all cases it was diagnostic of lung disease.

Wasserburger and associates (5), in an excellent study of 150 patients known to have emphysema and selected on the basis of moderately to markedly abnormal results with pulmonary function tests, found a vertical QRS axis to be an important and virtually constant characteristic of the electrocardiogram; only 3 patients (1.5 per cent) had "a nonvertical heart." Our results to date are at variance with those of Wasserburger *et al.*, possibly because the cases in Part I (1) were not preselected and because the electrocardiograms in Part II (2) and the present study were interpreted before it was known that the patients had lung disease. In Part I (1), fully 43 per cent of 79 consecutively admitted patients with lung disease (all degrees of severity) had ECG's without vertical or "axis-illusion" QRS axes. In the present group 14 patients (39 per cent) had ECG's with nonvertical QRS axes, *viz*, 7 with intermediate (+40° to +60°) axes and 7 with horizontal (−30° to +30° axes (Figs. 2, 3 and 4)). Furthermore, 5 of these patients had markedly reduced pulmonary function (Table 1, Nos. 1, 5, 20, 25 and 32), and in one (No. 32) the chest x-ray film suggested right ventricular enlargement.

Strictly speaking, the QRS *axis* must be distinguished from *electrical position*, which is plotted from the similarity between QRS configuration in unipolar extremity and precordial lead tracings (*e.g.*, the resemblance of aVF to V_6 and aVL to V_1 defines an electrically vertical heart, regardless of the orientation of the mean frontal QRS axis). In this sense, a vertical or semivertical electrical heart *position* was observed in every case, even in the 2 patients (Nos. 26 and 34) with x-ray evidence of left ventricular enlargement and the 14 patients with leftward or horizontal QRS *axes* (Fig. 3). Regardless of QRS orientation, however, the P-wave axis was always vertical. (A vertical P axis was found in 83

TABLE 1

Clinical Data			Electrocardiographic Criteria					Pulmonary Function				Roentgen Findings	
Patient		Pulmonary diagnoses	Axes		+ − P wave to V_2 or beyond	2 mm. S wave to V_5 or beyond	Gothic P wave	Vital capacity (*liters*)	Vital cap. (% of predicted)	1 second vital capacity (%)	MBC (%)	Lungs abnormal	Heart abnormal
No.	Sex & Age		P	QRS									
			(degrees)										
1	M68	Emphysema; bronchogenic ca.	+90	−30	+		+	2.80	73	42	—	+	0
2	M79	Emphysema	+80	+70	+	+		2.02	59	42	31	+	0
3	M41	Emphysema; fibrosis	+90	+70		+		3.42	81	48	50	+	0
4	M73	Emphysema; bronchiectasis	+80	+100	+	+		2.65	77	59	50	+	0
5	M77	Chr. bronchitis; emphysema	+90	+30	+	+	+	1.35	41	43	—	+	0
6	M57	Emphysema	+80	+60	+		+	3.70	97	68	79	+	0
7	M66	Emphysema	+70	+ 40	+		+	3.12	83	46	44	+	0
8	F66	Bronchiectasis; fibrosis	+80	+60	+	+	+					+	0
9	M52	Bronchitis; fibrosis	+70	+40	+							+	0
10	F58	Asthma; fibrosis; emphysema	+90	+100	+	+	+					+	? RV enlargement
11	F26	Hamman-Rich syndrome	+80	+80		+		1.14	33	80	45	+	? RV enlargement
12	M61	Silicosis; chr. bronchitis	+90	+80	+	+		2.78	73	42	40	+	0
13	M51	Emphysema	+90	+90		+	+	1.80	49	42	17	+	0
14	M57	Emphysema; fibrosis	+80	+100		+	+	1.09	31	50	—	+	0
15	M50	Bronchiectasis; emphysema	+90	+100		+	+	2.55	75	26	24	+	0
16	M66	Bronchogenic ca.	+80	+50	+							+	0
17	M48	Fibrosis; ? pneumoconiosis	+80	+30			+	3.84	86	40	48	+	0

18	M48	Bronchitis; emphysema	+80	+80		+	+	3.27	87	43	54	+	RV enlargement
19	M61	Bronchitis; emphysema	+90	+80	+	+	+	2.23	61	22	19	+	RV enlargement
20	M55	Bronchogenic ca.	+90	−30	+	+		1.67	43	41	—	+	0
21	M55	Bronchogenic ca.; left pneumonectomy	+80	+30			+	2.22	61	61	63	+	0
22	M54	Emphysema	+80	+70		+	+	3.36	87	43	47	+	0
23	M79	Asthma; emphysema	+80	+60		+	+	2.09	67	25	—	+	0
24	M67	Bronchiectasis	+70	+80	+	+	+	2.51	69	39	33	+	0
25	M66	Chr. bronchitis; emphysema	+80	+60	+	+	+	1.23	37	57	—	+	0
26	F67	Emphysema	+70	+60	+	+	+					+	LV enlargement
27	M50	Emphysema	+80	indeterminate	+	+	+	2.82	71	44	28	+	0
28	F54	Emphysema	+80	+70		+	+	1.81	65	44	72	+	0
29	M38	Emphysema	+80	+100	+	+	+	1.37	31	55	19	+	0
30	M55	Tuberculosis	+70	+70		+	+	4.30	111	—	127	+	0
31	M44	Bronchogenic ca.	+90	+80	+	+						+	0
32	M45	Asthma; emphysema	+80	−10	+	+	+	2.44	60	38	24	+	?RV enlargement
33	M40	Fibrosis; emphysema	+70	+80		+	+	.71	36	82	19	+	0
34	M55	Mult. myeloma; pulm. metastases	+90	+90	+	+						+	LV enlargement
35	M57	Emphysema	+80	+80	+	+	+	.76	21	59	—	+	0
36	M33	Tuberculosis; pleuritis	+80	+80		+	+	2.10	47	—	64	+	0
37	M46	Emphysema; bronchogenic ca.	+70	+30	+	+	+					+	0

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per cent of non-selected lung patients in Part I of this study (1), and a P axis of +50° or less was almost always a sign of additional disease associated with left heart strain.)

SUMMARY AND CONCLUSIONS

Of 200 patients in whom the diagnosis of diffuse lung disease was indicated by the electrocardiographic findings and confirmed by clinical, roentgen and pulmonary function data, 37 had ECG tracings which were normal by standard criteria. The characteristic finding was a vertical P axis (present in each case) with or without morphologic changes in the P waves. QRS orientation was not nearly so characteristic, although vertical QRS axes were present in 61 per cent of the patients.

Changes in P-wave axis and P-wave morphology are effective electrocardiographic criteria for the diagnosis of diffuse lung disease in adults. Since lung disease can be detected in a large group of patients by interpretation of this ostensibly normal ECG tracing, it would appear that these electrocardiograms are, in fact, abnormal.

The findings of the present study provide further support for a new electrocardiographic diagnosis, "consistent with diffuse lung disease." They also indicate that the applicability of electrocardiographic criteria for the detection of lung disease extends beyond the interpretation of tracings that are unequivocally abnormal.

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THE ELECTROCARDIOGRAM IN AGED PUERTO RICANS

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This report is part of a complete cardiovascular study performed on 322 aged Puerto Ricans. A comparison of the electrocardiographic findings with those of other investigators seems pertinent.

REVIEW OF THE LITERATURE

A perusal of the literature on the electrocardiograms of elderly persons is enlightening, although several questions remain unanswered.

Should the criteria for a normal electrocardiogram (ECG) in young adults be revised when applied to the aged? Do the changes represent the normal process of senescence or do they represent pathologic modifications with or without clinical significance? Are they based on biologic factors related to the onset and process of senescence? Is the electrocardiogram useful as a prognostic tool?

Willius (1) in 1931 was one of the first to report on the electrocardiogram in old age. The electrocardiograms of 700 patients, 75 years of age and older, revealed frequent extra systoles, especially of ventricular origin.

Two years later Dagnini (2) described left ventricular predominance in the aged, without hypertension and without radiologic evidence of left ventricular hypertrophy.

In 1938 Duthoit and collaborators (3) reported only 3 normal electrocardiograms for 116 subjects over 60 years of age. Evidence of frequent ventricular extra systoles and bundle-branch block predominated.

In 1941 Eliaser and Kondo (4) observed abnormal tracings in 85 of 100 octogenarians in apparently good health. The anomalies consisted of left axis shift, low voltage, sinus bradycardia, and prolonged P-R intervals.

Fox, Klements and Mandel (5) in 1942 reported 100 normal tracings in 300 persons between the ages of 60 and 90.

After the introduction of unipolar limb and precordial lead techniques, Wosika and associates (6) in 1950 reported abnormal tracings in 70 of 100 persons aged 80 years and older.

In 1957, Fisch and co-workers (7) found a high percentage of abnormal electrocardiograms among those of 500 patients studied; 141 of these patients were 80 years of age or more. They also reported that the percentage of abnormal tracings increased with age. Thus, in the 70–75 age group, 34.8 per cent of the records were abnormal; in the 80–85 age group, 46.7 per cent; and in the 90–95 age group, 75 per cent. For this series of 500 persons, 43.2 per cent of the ECG tracings were normal; 16 per cent showed occasional premature systoles; and 17 per cent showed nonspecific ST-T changes. Right bundle-branch block was indicated in 31 persons (6 per cent), prolonged P-R intervals in 21 (4.2 per cent), left bundle-branch block in 15 (3 per cent), prolonged intraventricular

conduction in 12 (2.4 per cent), and evidence of old myocardial infarction in 12 (2.4 per cent). Auricular tachycardia was noted three times, nodal rhythm twice, and A-V dissociation and wandering pacemaker once each.

Taran and Szilagyi (8) in 1958 found only 69 normal tracings among those for a series of 602 persons whose ages ranged between 65 and 95 years.

In 1957, Gelfand (9) studied 25 octogenarians and found that two-thirds of their electrocardiograms were abnormal in the absence of clinical manifestations of cardiovascular disease. He questioned the usefulness of the electrocardiogram as a prognostic tool.

Bonard and Sears (10) in 1958 reported a study of 208 ambulatory persons born in or before 1878 (they were therefore 80 or more years old); they found normal electrocardiograms in only 65 (31 per cent), and concluded that the electrocardiogram was of little value as isolated evidence for prognosis in surgical cases.

MATERIALS AND METHODS

All 322 subjects were aged 80 or older. There were 36 nonagenarians and 5 centenarians. Group I consisted of 52 healthy inmates of an Old Peoples Charity Home in Puerta de Tierra; Group II consisted of 270 patients referred to us for diagnosis and treatment, or for cardiovascular evaluation prior to surgical intervention.

There were 32 men and 20 women in Group I, and 142 men and 128 women in Group II. All were white, except for 5 in Group I, and 17 in Group II. All social, economic and racial strata were represented, but the majority of the subjects belonged to the higher social and economic levels.

TABLE 1

The Electrocardiogram in 322 Puerto Ricans 80 Years of Age and Older

	32 Healthy Men of Group I	20 Healthy Women of Group I	270 Patients Group II
Left axis shift	14 (44%)	10 (50%)	182 (67.4%)
Right axis shift	0	0	2
ST changes	6 (18%)	2 (10%)	84 (28.8%)
Low or diphasic T-waves	15 (47%)	3 (15%)	—
Conduction defects	9 (28%)	8 (40%)	—
Auricular fibrillation	4	1	25 (9.5%)
Left ventricular hypertrophy	7 (20%)	5 (50%)	42 (16%)
Right ventricular hypertrophy	0	1	2
Myocardial infarcts:			
Recent	0	0	8
Old or suspected	2	2	16 (9%)
Auricular premature beats	1	2	24 (9%)
Ventricular premature beat	4	3	8 (2.9%)
Left bundle-branch block	2	1	18 (6.6%)
Right bundle-branch block	1	1	22 (8%)
Sinus bradycardia	0	1	6 (2.2%)
Heart block, 2:1	1	1	2
Normal	*12 (37%)*	*7 (35%)*	*68 (25%)*

At least one technically acceptable twelve-lead electrocardiogram was obtained on each subject. The tracings were carefully measured, interpreted and analyzed.

RESULTS

Table 1 and Figure 1 show the results obtained in this study.

Contrary to the findings in childhood and youth, the predominant abnormality was a left axis shift. A right axis shift was rarely, if ever, seen. Electrocardiograms showing left axis shift were found in 14 of the 32 apparently healthy men, in 10 of the 20 apparently healthy women, and in 182 of the 270 persons referred for evaluation, diagnosis or treatment.

Alterations in the ST segment and T-waves were observed rather frequently. ST changes consisted mainly of depression. The change in T-waves was usually diminished voltage. The depression of the ST segments could be attributed to administration of digitalis in 24 of 270 patients. The T-wave changes were not significant; many appeared isoelectric and a few were diphasic.

Several authors have stressed the electrocardiographic evidence of left ventricular hypertrophy in the aged. Although there is no definite correlation between the postmortem findings and the radiologic and electrocardiographic manifestations of either left or right ventricular hypertrophy, the electrocardiogram is useful in suggesting, if not establishing, a diagnosis.

We considered the finding of at least one of the following criteria, as given by Taran and Szilagyi (8), to be suggestive of left ventricular hypertrophy: 1) the

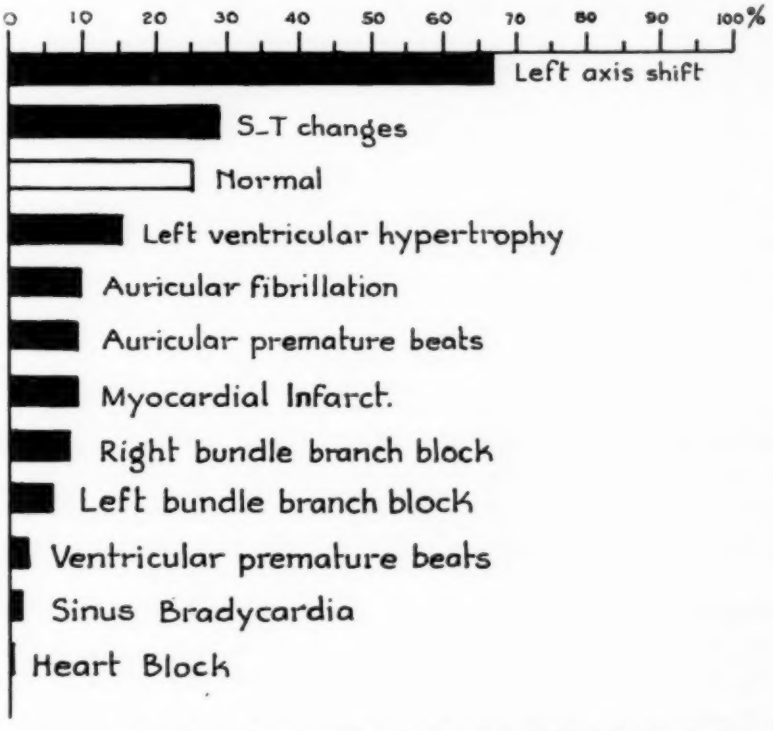

FIG. 1. Frequency of various electrocardiographic changes in 322 elderly Puerto Ricans

sum of the amplitude of R_1 and S_3 exceeding 24 mm.; 2) the amplitude of R wave in VL exceeding 11 mm.; 3) the sum of the amplitude of R in V_5 and S in V_1 exceeding 35 mm.; 4) the amplitude of R in V_5 exceeding 24 mm.; 5) the interval from onset of R to its peak, 0.04 second or more in V_5; and 6) the activation time exceeding 0.05 second in V_5.

There was electrocardiographic evidence of left ventricular hypertrophy in approximately 16 per cent of the cases, but practically no evidence of right ventricular hypertrophy.

Auricular fibrillation was present in 4 of the 32 healthy old men (12.5 per cent), in 1 of the 20 healthy old women (5 per cent), and in 25 of the 270 patients (9.5 per cent).

Evidence of recent myocardial infarction was not observed in the 52 apparently healthy subjects of Group I, but it was seen in 8 of the 270 patients in Group II. Evidence of old or suspected myocardial infarction was observed in 4 subjects (2 men and 2 women) of Group I, and in 16 patients of Group II. Thus myocardial infarction, recent, old or suspected, was noted in 9 per cent of the 270 patients in Group II.

It is noteworthy that, in general, auricular premature beats were far more frequent than ventricular premature beats. In the healthy men, nevertheless, we found more cases of ventricular premature beats (4) than of auricular premature beats (1). Among the 20 healthy old women, 2 had auricular, and 3 had ventricular premature beats. Among the 270 patients of Group II, 24 (9 per cent) had auricular permature beats, but only 8 (2.9 per cent) had ventricular premature beats.

Among the 270 patients of Group II, 22 (8 per cent) had right bundle-branch block, and 18 (6.6 per cent) had left bundle-branch block—a slight predominance of the former. There were no significant differences in this respect among the members of the smaller group of 52 healthy elderly persons.

Sinus bradycardia was not observed among the 32 apparently healthy men. It was seen in 1 of the 20 healthy aged women, and in 6 (2.2 per cent) of the 270 patients of Group II. In Group II we also found 2 cases of 2:1 heart block and 1 case of nodal bradycardia.

DISCUSSION

Warthin (11), among other authors, believed that in aged persons atrophy of the myocardium is the most probable natural terminal lesion, since the dominant features in senescence are a gradual slowing of metabolic processes, gradual desiccation of tissue, loss of tissue elasticity, atrophy, and degeneration. The problem of how these features affect the electrocardiogram remains to be solved.

There is great discrepancy between the results of studies on abnormal electrocardiograms in the aged. The frequency varies from zero in the small series of 50 cases reported by Jensen, Smith and Cartwright (12) to 98 per cent in the series of 116 cases reported by Duthoit, Warembourg and Pinchart (3).

We agree with Gelfand (9) and other observers that cardiac arrhythmias in

elderly persons may be an early sign of heart failure. It is our impression that frequent auricular premature beats often merge into auricular fibrillation and that frequent ventricular premature beats may be an early sign of congestive heart failure in the aged.

SUMMARY AND CONCLUSIONS

The literature on electrocardiographic changes in the aged has been reviewed and the results compared with those obtained by us in a study of 322 Puerto Ricans, aged 80 years or older.

In the present study, normal electrocardiograms were found in 37 per cent of 52 apparently healthy elderly subjects, and in only 25 per cent of 270 elderly patients. In the entire series of 322 persons the proportion of normal tracings was 27 per cent.

Left axis shift was the outstanding abnormality (67.4 per cent); right axis shift was extremely rare.

Auricular premature beats were more frequently noted (9 per cent) than ventricular premature beats (2.9 per cent).

Electrocardiographic evidence of left ventricular hypertrophy was found in 16 per cent of the cases, but evidence of right ventricular hypertrophy was extremely rare.

There was a slight predominance of right (8 per cent) over left (6.6 per cent) bundle-branch block.

Electrocardiographic evidence of recent myocardial infarction was found in only 8 (3 per cent) of the 270 patients and in none of the apparently healthy elderly persons.

Evidence of old, healed or suspected myocardial infarction was present in approximately 9 per cent of the total series.

Sinus bradycardia was found in only 2.2 per cent of the cases.

The hypothesis is advanced that frequent auricular premature beats may precede the appearance of auricular fibrillation, and frequent ventricular premature beats may be early evidence of congestive heart failure in the aged. Additional observations and more detailed study are required.

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EXPERIENCES WITH FURALTADONE IN A CHRONIC DISEASE HOSPITAL

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The increasing prevalence of uncontrolled infections in hospitals emphasizes the urgent need for investigating new, effective antibacterial agents.

In studies made in a hospital for chronic diseases where the dangers of these infections are particularly great, the following causative factors were observed:

1) loss of antistaphylococcal effect of some antibiotics, *e.g.*, penicillin, the tetracyclines and streptomycin, probably because of the increasing development of resistance to bacterial drugs. During the past year, when the use of penicillin in our service was restricted, some staphylococcal strains became susceptible to this drug;

2) the advanced age of most patients with chronic disease, many of whom are admitted with degenerative disorders and loss of natural resistance;

3) extensive surgical and medical procedures which interfere with the resistance of the host;

4) increasing survival of seriously ill patients and those with such diseases as multiple sclerosis, parkinsonism, paraplegia or cancer, constituting a class of patients highly susceptible to infection;

5) hospital-acquired infections resulting from poor resistance, faulty sterilization technic, improper instrumentation, improper dressings or laundering, carriers among hospital personnel and the indiscriminate use of antibiotics;

6) diabetes;

7) urinary-tract infections (found in 10 to 15 per cent of autopsies, and three times more common in men than in women);

8) metabolic disorders such as malnutrition, steatorrhea, ulcerative colitis or allergies;

9) acute and subacute bacterial endocarditis and heart failure;

10) collagen diseases;

11) superimposed infections with alterations of the intestinal flora;

12) systemic conditions predisposing to reinfection, *e.g.*, sarcoidosis, cirrhosis, leukemia or lymphomatosis.

There is urgent need for a new, effective antibacterial agent, and its development requires careful study and investigation. Chemotherapeutic agents have certain disadvantages when compared with antibiotics; yet we must remember that modern therapeutics stems from Ehrlich's Salvarsan, a chemical agent. The aim of chemotherapy is the eradication of infection by means of inhibiting the growth and proliferation of the causative organism. Even when this goal

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is achieved, complete recovery still depends upon the body's mechanism of defense. Hanell's basic formula represents this concept best:

$$\frac{\text{No. of bacteria} \times \text{virulence}}{\text{body resistance}} = \text{severity of infection.}$$

Results of controlled animal experiments with a chemotherapeutic agent are not the final word. Chemotherapy has usually been empiric and a knowledge of the drug's exact mode of action, though desirable, is not indispensable: the response of the patient is the final criterion. Examples of empiric chemotherapy in the past are: quinine for malaria, mercury for lues, and ipecacuanha for amebiasis. Ehrlich's hope for a chemical disinfecting agent, capable of complete destruction of the invading organism is still to be realized.

In view of the foregoing considerations, a purely clinical evaluation was conducted with furaltadone,[1] a synthetic antibacterial agent. Its action is postulated to be inhibition of enzymatic systems in the carbohydrate metabolism of the bacteria in the Krebs-cycle stage (1). High blood levels are not attainable with this drug, but good *in vivo* results are obtained because of optimal tissue concentrations. The tissues act as their own concentration regulators to prevent toxic levels. The mechanism is not clearly established, but the point to be emphasized is that the pathologic process primarily affects tissues, so that the ultimate goal of therapy lies in the response of the patient. It is significant that bacteria can develop only limited resistance to the nitrofurans (2).

MATERIAL AND METHODS

In the interests of accurate evaluation, the drug was not prescribed for patients with cirrhosis of the liver, peptic ulcer or gastritis (present or past). Consumption of alcohol is a contraindication to furaltadone therapy, but in our hospital this problem did not exist. The average peroral dosage of furaltadone was 250 mg. four times daily, and the duration of treatment was from two to twenty-five days, with an average of six days.

Diagnoses were as follows: pyoderma and mastitis 45 cases, otitis media and externa 2, bronchopneumonia 7, bartholinitis 1, pyelonephritis 1, infectious arthritis 1, acute thrombophlebitis 1, empyema 1, and perinephric abscess 1.

In the 45 patients with dermatologic infections (abscesses, decubital ulcers, cellulitis, carbuncles, furunculosis) the causative organism was Staphylococcus aureus, coagulase positive, sensitive to furaltadone.

Sixty patients with severe or resistant infections were treated with furaltadone. In the early studies, the drug was given only after antibiotic therapy had failed. As more confidence in its use was gained it was employed in an increasing scale not only alone but, in some instances, combined with other agents not clinically antagonistic. Most cases, however, were treated with furaltadone alone.

Whenever possible, cultures were made and the sensitivity of the pathogen was tested by the disc method, using 50 μg. of furaltadone and standard antibiotic discs. The diagnosis was made on the basis of clinical criteria, and was confirmed by laboratory tests and x-ray examination when required. Complete hemograms, differential blood counts and urinalyses were made before, during and after the acute infection.

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[1] 5-Morpholinomethyl-3 [5-nitrofurfurylideneamino]-2-oxazolidinone.

RESULTS

Clinically there were 42 (70 per cent) cures, 6 (10 per cent) improvements and 6 (10 per cent) failures; in 6 cases (10 per cent) the results were inconclusive. Among the 6 failures there were 3 deaths—from diabetes and uremia, diabetes and intestinal gangrene, and parkinsonism and urinary infection, respectively.

The drug proved particularly effective in the treatment of skin infections. The favorable results could be attributed to careful selection of the drug, adequate length of treatment, daily close observation and laboratory cooperation. They were even more significant in view of the fact that these patients suffered from chronic primary conditions and had failed to respond to antibiotic therapy.

Bacteriologic cultures were made in 47 cases; in 36 the results were positive, with Staphylococcus aureus predominant. In 13 cases no cultures were made, since the patients had closed nondraining lesions; in nearly all these cases, response and resolution of the lesions were excellent, and therefore cultures at a later date were not required.

In only 4 (7 per cent) of the patients was it necessary to discontinue the drug—in 2 because of generalized pruritus and in 2 because of vomiting. Other than these, only minor side-effects were observed (3 cases of nausea and vomiting); these subsided quickly upon cessation of therapy. Criteria for discontinuance of treatment were alterations in the white blood cell count, vomiting, diarrhea or urticaria. Two of the patients tolerated doses as large as 500 mg., but not for more than forty-eight hours. No hematopoietic or neurologic toxicity was observed. Severe side-effects (similar to those reported in the literature) occurred only in cases in which the dosage far exceeded the recommended maximal daily amount, and when the drug was given for prolonged periods of time.

TYPICAL CASE HISTORIES

The following 2 cases are illustrative:

Case 1

This 52-year-old man had suffered from parkinsonism for many years. In August 1959, a diagnosis of empyema of unknown cause was made and confirmed by the results of x-ray examination and thoracentesis. He received penicillin, streptomycin and chloramphenicol, with no improvement. In February 1960, open surgical drainage was performed; his postoperative course was complicated by remittent fever and a thoracic fistula with a copious discharge of pus. A culture showed Staphylococcus aureus and Streptococcus beta hemolyticus. The patient again received penicillin, streptomycin and then chloramphenicol, with poor results. Furaltadone became available in April. The organisms were found to be sensitive to this drug and the patient was then given furaltadone perorally in a dosage of 250 mg. four times daily for nine days. His fever subsided and the fistula closed; roentgenograms of the chest showed markedly diminished opacity.

Case 2

A 60-year-old woman also had had parkinsonism for many years. In May 1960, fever developed and physical examination showed a hot tender area over the right lower flank,

containing pus. X-ray studies disclosed a fistula leading to the area over the right kidney, with obliteration of the psoas muscle. The presence of Staphylococcus aureus was confirmed by culture, and the patient was given 250 mg. of furaltadone four times daily, perorally, for twenty-one days. The fever subsided rapidly, the drainage ceased, and the fistula closed. To date there has been no recurrence.

SUMMARY AND CONCLUSIONS

A new antibacterial nitrofuran, furaltadone, was used in the treatment of 60 patients with chronic diseases complicated by infections, mostly staphylococcal and refractory to antibiotic therapy.

Forty-two patients (70 per cent) were cured both clinically and bacteriologically, 6 (10 per cent) were improved, and in 6 the results were equivocal. There were 6 failures.

Side-effects occurred in only 4 patients, but they were minimal and easily controlled by cessation of therapy. No hematopoietic, gastro-intestinal or neurologic toxicity was observed, probably because of careful selection of patients, and proper dosage and duration of treatment.

Hospitals for chronic diseases are urgently seeking new and safer drugs to combat the increasing number of infections unresponsive to conventional therapy. Each new antibacterial agent effective in the treatment of these infections is always potentially valuable and warrants clinical trial. Our results with furaltadone have been most encouraging and indicate the usefulness and safety of this new chemotherapeutic agent.

Addendum

Since completion of this study, some untoward reactions have been reported. Loftus and Wagner (3) described in 2 patients a new allergic reaction characterized by diplopia. After discontinuance of medication, the diplopia gradually resolved. One patient had been treated for fifty-nine days, and the other had been treated intermittently from September 3, 1959 to January 9, 1960. The doses these authors employed are far greater than those we prescribed.

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TREATMENT OF DIABETIC RETINOPATHY WITH ESTROGENS

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The management of diabetes with retinopathy and recurrent intraocular bleeding poses a frustrating challenge to both the internist and ophthalmologist, notwithstanding skillful attention to the patient's general medical status and the local eye complications. The limitations of current treatment are exemplified by the total of five short paragraphs—essentially negative in nature—devoted to this subject in recent editions of two textbooks on diabetes (1, 2).

Drug therapy. Criticism directed toward drug therapy in the management of diabetic retinopathy is justifiable, in view of the initial, but transient, enthusiasm for the host of agents that have failed to live up to the claims made for them (3–10). Furthermore, one has to consider wide variations in the rate of resorption of intraocular hemorrhages.

The following excerpt from a recent review (11) of the ocular complications in diabetes presents the attitude currently shared by most clinicians and ophthalmologists: "When these hemorrhages extend into the vitreous body, they stimulate a proliferation of capillaries and fibroblasts; the eventual contraction of this fibrous tissue is often the cause of retinal detachment. This extensive neovascularization (retinitis proliferans) is often severe enough to cause blindness even when it is confined to the retina. . . . Some ophthalmologists believe that all the changes may progress and regress spontaneously, except that retinitis proliferans itself is almost always irreversible. Obviously, the best treatment will be that which prevents the appearance of neovascularization and induces regression of the other lesions. Such an ideal treatment is not yet available."

In another recent review (9) the following statement is made. "There is good evidence that rutin and other orally administered flavonoids are destroyed by the intestinal flora. Also it has been found that administration of rutin, esculin and adrenoxyl intravenously has no effect on capillary fragility. All in all, treatment of diabetic retinopathy with preparations aimed at decreasing capillary retinal hemorrhage has been disappointing."

When the magnitude of the problem of diabetic retinopathy—as reflected by the continuing and striking increase in the incidence of diabetes among the blind—is viewed in the light of the relative inadequacy of current therapy, any reasonable claim regarding an effective therapeutic agent merits attention and trial by other observers. In the United States alone, for example, it is estimated (12 *a*) that there were approximately 28,000 blind diabetics in 1957 as compared with 3,200 in 1940. This rising incidence of blindness due to diabetes also has become apparent in England (12 *b*), as manifested by an increase within the 50–69 year age group from 8.4 per cent for the 1949–1950 period to 13.3 per cent

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for the 1951–1954 period. In large measure, this increase is due to the prolonged survival of diabetics in the past few decades.

Hormonal therapy. The status of certain surgical procedures in the management of diabetic retinopathy remains to be established. A potential exists for its dramatic amelioration, however, following bilateral adrenalectomy, pituitary failure (14) or hypophysectomy (15). Vannas *et al.* (16 *a*) noted that, in a series of 10 patients with diabetic retinopathy, after hypophysectomy there was a tendency toward regression of venous and capillary dilatation and the micro- and macro-aneurysms, along with absorption of existing hemorrhages, diminution of active bleeding, diminution in the rate of proliferation, and disappearance of waxy exudates and cotton-wool patches. (In 3 of the patients, however, there was deterioration of vision in the remaining eye postoperatively because of new hemorrhages.) The Joslin group (1), after occasionally observing improvement post partum in a patient with advancing retinopathy during the preceding pregnancy, temporarily tried progesterone in the treatment of other diabetic patients with retinitis proliferans. Field *et al.* (16 *b*) recently reported upon the efficacy of hypophyseal stalk section in arresting diabetic retinopathy. This procedure was followed by cessation of hemorrhagic activity and regression of aneurysmal lesions, proliferative tissue and neovascularization. An effect upon a humoral factor of hypothalamic or pituitary origin was postulated.

The present report sets forth the author's experiences relating to the beneficial action of estrogens (administered orally or intravenously) in the control and prevention of recurrent hemorrhage in diabetic retinopathy after other conservative measures had proved unsuccessful. Although the series of patients is small, the observations appear to be valid, since they were based upon the comparison of the clinical course before, during and after estrogen therapy, and during placebo administration.

METHODS

Nine patients with symptomatic diabetic retinopathy were studied.

For the purpose of uniformity, only one estrogen was employed. The preparation used orally was Premarin[1] (conjugated estrogens, equine) 0.3 mg. to 1.25 mg. daily. Male patients received a dosage below that which might induce gynecomastia. Patients are apt to tolerate large doses of Premarin better than other estrogenic preparations with regard to gastric distress, nausea and general discomfort. On the other hand, the effects on the breasts, sexual desire and sexual function are virtually the same with equivalent doses (17). In several postmenopausal patients, the dosage was kept small or the hormone was omitted cyclically for brief periods to obviate vaginal bleeding. Small dosages also were employed in patients with known cardiac or renal involvement in order to minimize edema, though unfortunately it was not always possible to avert this complication.

The preparation employed for injection was Premarin Intravenous[1], the usual dose being 20 mg. This agent is available in the form of individual "Secules," each containing 20 mg. of estrogens in a naturally occurring water-soluble conjugated form (expressed as sodium estrone sulfate). Shortly before administration, the estrogen is put into solution by adding 5 ml. of sterile diluent containing 0.5 per cent phenol U.S.P. from the accompanying vial. The resulting clear solution remains stable for periods of from sixty to ninety days at room

[1] Kindly supplied by Ayerst Laboratories, New York City.

temperature if not exposed to light. The solution should be injected slowly, to prevent the occurrence of flushes.

The author has acquired an extensive experience with the use of this preparation in the management of bleeding episodes in patients being maintained with long-term anticoagulant therapy (18), in severe gastro-intestinal hemorrhage, in cirrhosis of the liver, in severe prostatism, and in patients seriously ill with congestive heart failure, myocardial infarction or stroke (19). When given as directed, no serious side-effects have been noted. Neither allergic reactions nor inflammatory responses in the tissues were observed. Other investigators have injected Premarin intravenously in amounts up to 500 mg. within a 24-hour period without demonstrable deleterious effects (20).

In one patient (Case 3) with the nephrotic syndrome due to diabetic glomerulosclerosis and acute massive bleeding into one eye, it was necessary to confine therapy to the intravenous route because dyspnea and anascarca were promptly increased when small doses of estrogens were taken orally. (Similarly, in cases of chronic liver disease and nasal telangiectasia, recurrent bleeding has responded promptly to intravenous estrogens without the edema attendant upon oral administration.) Others have noted the unique intolerance to small amounts of estrogens in some patients with cardiac disease, promptly manifested by heart failure (21). The absence of hyperestrogenic effects and significant retention of sodium chloride and water with intravenous administration can be explained by the rapid metabolism of the drug and its conversion into nonactive metabolites (22).

In patients having retinopathy without bleeding who exhibited significant subjective improvement in vision during long-term estrogen therapy, the medication was withdrawn or placebo tablets (identical in appearance to the active preparation) were administered. In the course of several weeks, there was an exacerbation of symptoms in several such patients (Cases 4, 5, 6 and 7). In order to minimize errors related either to bias or to anxiety on the part of the patient, the testing of vision was performed in the standard manner by a trained nurse.

All patients in this study were seen in the author's private and consultation practice. The majority were observed concomitantly by one or two ophthalmologists. Most of these patients previously had been given large doses of vitamin C, vitamin K, bioflavonoids, crystallized trypsin, and a variety of other medications by ophthalmologists and clinicians—without demonstrable benefit. At the time the hemorrhages occurred, most were taking vitamin C and vitamin K, as well as supplemental multivitamin preparations.

The pathology underlying the impaired vision of patients in this series was primarily that of diabetic retinopathy with or without retinal bleeding (more accurately termed "oozing"), rather than cataract formation, optic neuritis or optic atrophy. The inability to make this distinction solely on the basis of an ophthalmoscopic examination is indicated by the considerable number of patients with severe lens opacities who manage to maintain satisfactory vision, and by the occasional patient who experiences subjective improvement in vision despite progressive retinal changes noted ophthalmoscopically.

Several other rules for management were routinely followed *prior to* the oral administration of estrogens in patients not having active bleeding. Thus an attempt was made to establish a baseline standard of vision during routine comprehensive medical management and to counterbalance the potentially confusing factor of a new physician expressing interest in the patient's problem.

When the patients initially had retinal bleeding, the following regulations and measures were instituted in addition to intravenous estrogen therapy:

1. *Rubbing of the eyes was strictly prohibited.* The author (an internist) is impressed by how rarely these patients are specifically told not to rub their eyes, as many habitually do.
2. *Excessive smoking was not allowed.*
3. *Parenteral vitamin B_{12} was prescribed.* This substance is innocuous and is excreted in smaller amounts in the urine of diabetic patients with retinopathy than in normal persons or in diabetics with no complications (10).
4. *Hypoglycemia was prevented or minimized.* These patients tend to manifest fewer

clinical complications of retinopathy when the dosage of insulin is reduced. Therefore, the patients whose blood sugar levels fluctuated markedly were advised to avoid taking insulin too long before a meal. In several instances, it also was recommended that the patient awaken in the early morning hours for a snack.

5. *Elevation of the head of the bed* may prove beneficial in patients experiencing nocturnal vitreous hemorrhages, and occasionally was recommended. Keen (13) has suggested that the benefit is probably due to a reduction in intravascular pressure, notably resulting from hypoglycemia.

COMMENT ON MANAGEMENT

Intelligent patients repeatedly have informed me that they are more prone to have intra-ocular bleeding after a hypoglycemic attack or if their fasting blood sugar level is persistently low. It is generally acknowledged that there is often a precipitous rise in intra-ocular tension with associated visual disturbances during hypoglycemic attacks in diabetes (13). This phenomenon probably is related to changes in intraocular tension, which in turn influence the vessels and, in so doing, favor bleeding. Furthermore, excess insulin paradoxically can induce hyperglycemia and exacerbation of diabetes as manifested by extreme fluctuations of glycosuria and ketonuria. (The diabetic patient who adjusts his insulin dosage solely on the basis of the amount of glucose in the urine is particularly apt to encounter this difficulty.) Such impairment of carbohydrate tolerance might be explained by hypoglycemia-induced stimulation of the adrenal-pituitary system, with subsequent accelerated release of one or several hormones that raise the level of blood sugar (23). In fact, a significant rise in the concentration of plasma 17-hydroxycorticosteroids has been found in insulin-treated patients who become hypoglycemic, in contrast to those who do not become hypoglycemic (23b).

A great body of data can be used as evidence for a significant relationship between the incidence and severity of retinopathy and the degree of diabetic control (1). Admittedly, patients in whom diabetes is poorly controlled in association with multiple attacks of keto-acidosis are prone to a more rapid development of the retinopathy (9). Nevertheless, the repeated observation of conscientious young diabetics whose retinopathy has progressed in spite of their best efforts is sobering. Except for the fact that it takes an average of thirteen years for retinopathy to appear in juvenile diabetics, there is no clearcut relationship between the duration of diabetes and the incidence or severity of the retinopathy (24). Furthermore, an accurate biochemical or biologic definition of "control of the diabetic state" remains highly elusive. Perhaps the ultimate criterion for severity of the diabetic state will be related to the rate of glucose utilization by the tissues. This could explain such facts as the following: 1) patients in whom diabetes appears during early maturity secrete adequate amounts of insulin (as determined by the highly sensitive immuno-assay procedure of Yalow and Berson (25) for endogenous plasma insulin), the average integrated plasma insulin concentration during a two-hour glucose tolerance test being 26 per cent higher for diabetics than for nondiabetics; 2) there is no significant relationship between the severity of diabetes as gauged by insulin require-

ments and the incidence of neuropathy; and 3) the most severe neurologic syndromes often are observed in patients with mild or latent diabetes.

From the available evidence, it appears that the evolution of diabetic retinopathy is no more favorably influenced by the use of oral antidiabetic drugs than by the use of insulin. Moreover, an apparent acceleration of retinopathy in patients treated with antidiabetic sulfonamides who had received insulin previously, as compared with those without prior insulin therapy, has been observed in one clinic (26).

In reply to those objecting to such a de-emphasis of rigid diabetic management, it is noteworthy that Dolger (27), Friedenwald (28), and others who have devoted considerable attention to the problem of diabetic retinopathy have come to the general conclusion that the vascular lesions represent an integral part of the disease (*i.e.*, "concomitants" rather than "complications") and are not related to the blood sugar level *per se*. A similar special vulnerability of both the central nervous system and the vascular system in the diabetic may account for the frequency of the triad ("triopathy") of retinopathy, neuropathy and nephropathy.

RESULTS

In 7 of the 9 patients with symptomatic diabetic retinopathy, followed for periods up to three years, estrogen therapy was associated with improvement in the retinal lesions. The criteria for improvement included the following: 1) demonstrable cessation of active retinal bleeding, with or without resorption of hemorrhages; 2) no recurrence of bleeding in patients previously manifesting continual or repeated hemorrhage; 3) sustained objective improvement in vision; and 4) an exacerbation of visual impairment after withdrawal of estrogen or substitution of placebo therapy.

The most impressive results in this study were observed in cases of active hemorrhage and of slight to moderate degrees of retinopathy. The oral administration of estrogens over prolonged periods appeared to be of decided value both in reducing the incidence of recurrent hemorrhage and improving the vision of diabetics with retinopathy, provided adequate doses could be given without edema or vaginal bleeding. The effectiveness of intravenous administration of estrogens in promptly reducing or stopping intraocular bleeding after oral administration alone had been ineffective was observed repeatedly. The 2 patients who failed to respond had far-advanced retinopathy with retinitis proliferans and glomerulosclerosis.

Estrogens can produce anemia and aplasia of the marrow experimentally (29), but this has not proved to be a significant deterrent in treating patients with large doses of estrogens intravenously and moderate doses by mouth. Thrombocytopenia associated with estrogen therapy has been observed rarely by others (30) and not at all by the author.

The response to estrogens of 4 cases of diabetic retinopathy with bleeding and 3 cases without bleeding will be presented.

CASE REPORTS

Prolonged treatment with estrogens in the prophylaxis of episodes of retinal bleeding; improvement in vision

Case 1. *E. G.*, a 55-year-old white building inspector, was seen in consultation in September 1957 at the request of his referring ophthalmologist. A diabetic for more than thirty years, he had been using insulin faithfully since 1926. He was of normal weight, had always adhered to his diet carefully, and was taking two doses of Lente insulin daily (24 units before breakfast and 10 units before his evening meal.) On only one occasion (following an infection) prior to coming under my care had his condition approached clinical acidosis. Symptomatic diabetic retinopathy had developed several years previously, but he had become particularly disabled because of repeated hemorrhages in both eyes during the last two years. This difficulty had reached the point where he was unable to drive alone. He could barely read even large print, so that his job (largely entailing inspection of building plans) was in jeopardy. Many pharmaceutical preparations had been given in large doses and over prolonged periods by several internists and ophthalmologists in an attempt to control the ocular bleeding, including bioflavonoids (C.V.P.), vitamin K, and vitamin C—all without benefit.

Examination revealed the presence of vitreal hemorrhages, diabetic exudates, numerous micro-aneurysms, and slight lens opacities in both eyes. Over the course of several weeks, it became evident that the patient was experiencing frequent hypoglycemic attacks, particularly in the mid-afternoon and early morning. He repeatedly noted that he was more prone to increased ocular bleeding following severe insulin reactions. The insulin dosage was progressively lowered to 18 units in the morning and 5 units before the evening meal. Fasting blood sugar values remained at levels of 89 mg. and 75 mg. per 100 ml. A further reduction in the dosage of insulin, however, was attended by hyperglycemia and polydipsia.

The patient initially was given a revised diabetic diet, supplemented by multivitamins orally and vitamin B_{12} parenterally. Estrogen therapy (Premarin 0.625 mg. per day) was started by the oral route. Over the next two months, there were only a few hypoglycemic reactions and only two episodes of oozing hemorrhages within the eye. An increase in the dose of Premarin to 1.25 mg. daily induced gynecomastia, so the dosage remained at the initial level. The patient's vision improved over the next six months. He had two insulin reactions following the death of his mother; with each reaction there was slight intra-ocular bleeding for several days.

The patient fared well until November 1958, when he presented himself with persistent and considerable bleeding in the right eye, of one day's duration. He was given 20 mg. of Premarin intravenously. By the next day, he volunteered that he could detect no further bleeding. Along with an additional dose of Premarin intravenously, he received streptococcal enzymes (Varidase, buccal) several times daily. The ocular hemorrhages cleared promptly within the next few days. The oral estrogen therapy and the other supportive measures were continued. On numerous occasions, he observed that his vision was best when there was occasional slight glycosuria, and that an increase in the dosage of insulin promptly resulted in impaired vision. An attempt at control of the diabetes with tolbutamide (Orinase) was unsuccessful.

When examined fourteen months following the last significant ocular hemorrhage, the patient had no further bleeding into either eye, was working full-time, drove his car without difficulty, and even could read the fine print in the telephone directory. The dosage of Premarin had been reduced to 0.625 mg. twice weekly, to obviate gynecomastia. A number of serious family crises had arisen, but were handled without detriment to his diabetes or vision. The retinopathy (except for the absence of recent bleeding) remained unchanged ophthalmoscopically. The patient volunteered that his three-dimensional vision had improved during the previous six months, along with the improvement in sight in the right eye.

In January 1960, the patient had a severe upper respiratory infection, culminating in the development of acute diabetic acidosis. After admission to the hospital, the acidosis was readily controlled. Several hours after an insulin-induced hypoglycemic episode (as his insulin requirement diminished), the patient noted that his vision had deteriorated and was very cloudy. No new retinal bleeding was demonstrable, however. He had continued to take Premarin orally (0.625 mg. per day) from the time of admission. Several hours after a single intravenous injection of Premarin, visual clarity had returned completely.

This patient did not come back for his scheduled follow-up visits, because of pressing personal obligations. He continued with his program of insulin (20 units a.m., and 10 units p.m.), Premarin orally (0.625 mg. twice weekly), vitamin B_{12} twice weekly, and vitamins by mouth. He was able to distinguish various shades of color with increasing accuracy in the right eye during the next several months. His course was uneventful until April 1960, when he was involved in litigation and became extremely upset because he felt that legal counsel had caused him to lose his case. On arising the next morning, there was blood in the left eye and he could barely see. The patient refused to heed his wife's advice to get an injection of Premarin, and accordingly was not seen until June 2, 1960. He had continued with the same program of medication and in addition had resumed taking vitamin K by mouth. Vision in the left eye remained markedly impaired; long streaks of blood were visible to the patient. A considerable amount of blood was noted in the vitreous of the left eye; this prevented examination of the major part of the fundus. Premarin was administered intravenously that day and the next; then daily oral administration was resumed.

On June 6, 1960, the patient stated that there had been definite improvement in the clarity of vision in his left eye. He found he could read small newsprint. The vision in the left eye was 20/70. He was advised to reduce the dosage of insulin to 20 units in the morning and 8 units in the evening. A third injection of Premarin was given. Anti-inflammatory enzyme (Chymoral)[2] therapy was started in a dosage of 1 tablet four times daily. Vision remained cloudy for another week, but then improved greatly within a period of one day. He was able to do considerable reading and to analyze charts without difficulty. Examination on June 14, 1960, revealed marked clearing of the vitreous.

Improvement continued over the ensuing seven days, during which time he engaged in close and detailed reading without difficulty. Vision in the left eye was 20/40. He then noted a small amount of active bleeding while on his way to have his blood sugar level checked. There were no signs of hypoglycemia clinically; the fasting blood sugar level was 73 mg. per 100 ml. The bleeding promptly subsided after another injection of Premarin. A regimen of a reduced evening dose of insulin, a mandatory bedtime and 2-a.m. snacks was instituted. There had been no further bleeding several weeks later when he was last seen.

Treatment of continued retinal hemorrhage with estrogen

Case 2. *O. R.*, a 48-year-old colored female, was known to have had diabetes for over three years. The disease was complicated by coronary insufficiency, heart failure (compensated) and symptomatic retinopathy. The latter had become more troublesome, as manifested by decreasing vision in both eyes and also continual bleeding into the right eye. She had to discontinue self-medication with insulin because of her inability to read the syringe markings. Training for the blind was actively under consideration. An attempt to control her diabetes with tolbutamide was initially unsuccessful. Phenformin (DBI) therapy was then tried, and satisfactory control of the blood sugar was soon achieved.

When this patient was seen first, her vision had deteriorated to such a degree that she had to be accompanied during most activities. She could do no close reading. Administration of DBI in a dosage of 62.5 mg. (2½ tablets) daily was associated with hypoglycemic episodes, and retinal bleeding became more intense. Examination of the left eye revealed extensive and typical diabetic retinopathy, with retinitis proliferans. It was impossible to see the right fundus clearly because of the presence of blood in large amounts.

[2] Kindly supplied by Armour Pharmaceutical Company, Kankakee, Illinois.

On September 3, 1959, the patient was given Premarin (20 mg.) intravenously. She was counseled not to rub her eyes, and to reduce the dosage of DBI to 50 mg. daily. When next seen on September 10, 1959, she stated that she had been unable to detect any evidence of further bleeding for two days following the injection; then bleeding had recurred and had persisted. The patient was given another injection of Premarin, and the hormone was also started by oral administration (1.25 mg. daily). She had been taking digoxin, vitamins and vitamin B_{12} parenterally (for associated neuropathy of the lower limbs), and this medication was continued. Her fasting blood sugar level on September 10 was 156 mg. per 100 ml.

At the patient's subsequent visit on September 17, 1959, she stated that for the first time in more than one year there had been no ocular bleeding for a whole week. She further volunteered that she could see the "1 cc." marking on her syringe, so that she could inject her dose of vitamin B_{12}. She felt greatly improved in all respects; this was corroborated by a striking change in her appearance. No further bleeding was noted by the patient or upon ophthalmoscopic examination over the ensuing month, during which period she received weekly injections of Premarin supplementing a reduced oral dosage. She was seen in consultation by an ophthalmologist who previously had examined her. Although there was no demonstrable change in the proliferative retinopathy, he was impressed by the lack of bleeding in the vitreous and in the retina since the previous examination.

One month later, this patient entered the hospital because of congestive cardiac failure. Estrogens were discontinued at that time. The cardiac condition responded well to digitalis, chlorothiazide, restriction of salt, and other supportive measures. Subsequently, because of persistent urinary symptoms related to a large cystocele, the patient underwent reparative surgery; complete hysterectomy and bilateral salpingo-oophorectomy were also performed. She then was followed in the Cardiac Clinic. The diabetes was controlled with tolbutamide (Orinase, 0.5 Gm. daily) and a diabetic salt-restricted diet. The fasting blood sugar level, over a period of approximately five months, ranged between 109 mg. and 200 mg. per 100 ml.

About December 15, 1960, bleeding recurred in the right eye and persisted for approximately three weeks. (This was the first bleeding she had noted in approximately seven months after the previous estrogen therapy had been discontinued.) There was no vision in the left eye. She was given Premarin intravenously (20 mg. every five to seven days) and orally (0.3 mg. daily). Within a few days, she noted that there was no more "dripping" of blood in the right eye. The effect was comparable to the initial response about a year previously. She then noticed progressive improvement in vision, enabling her to read the newspaper headlines and some of the larger type. Visual studies revealed that she now was able to make out the top two lines of the Snellen chart with fair accuracy. By the end of the second week of estrogen therapy, bleeding had ceased and vision had improved markedly in the right eye. Moreover, there was a return of light perception in the left eye for the first time in a long period. Vision in the right eye was better than 20/100, and she was readily able to perceive a small flower pattern on the examiner's tie. There had been considerable clearing of the hemorrhagic material in the vitreous of the right eye. Cardiac status was maintained without weight gain.

Treatment of acute retinal hemorrhage with estrogen

Case 3. *H. B.*, a 50-year-old white male advertising executive, was known to have had diabetes since the age of 32. He had been taking a combination of 50 units of NPH insulin and 10 units of regular insulin for a number of years. In the course of extensive traveling, he had experienced several bouts of diabetic acidosis, each necessitating hospitalization. Following a urinary-tract infection, it was difficult to maintain him without hypoglycemic reactions, when using the previous dose of insulin. Therefore, the dose of NPH insulin was progressively reduced to 23 units daily.

When first seen in consultation on December 4, 1959, the patient had progressive dyspnea and anascarca of several months' duration. Physical examination revealed a regular pulse

of 100, blood pressure 130/82 mm. Hg, extensive diabetic exudates without hemorrhages in the ocular fundi, fluid in both lower lung fields, and marked enlargement of the liver extending throughout the epigastrium and right upper quadrant. The urine contained albumin. The serum nonprotein nitrogen level was 57 mg. per 100 ml. The diagnosis was diabetic glomerulosclerosis with the Kimmelstiel-Wilson syndrome and diabetic retinopathy. The patient also had arteriosclerotic heart disease with congestive failure. He was treated with a regimen directed toward improving cardiorenal function and reducing the edema, *viz*, restriction of fluids, administration of hydrochlorothiazide, an increased dosage of digitalis, parenteral vitamins (including vitamin B_{12}), bed rest, and readjustment of his diet and insulin dosage. The improvement was striking.

On December 15, 1959, the patient presented himself with an acute hemorrhage into the right eye. He stated that he had been getting along well until three days previously, when the hemorrhage had occurred after a bout of coughing. Since then, he had lost most of the vision in the right eye. Examination revealed the presence of extensive fresh hemorrhages, both medial and lateral to the optic disc, with one large retinal hemorrhage (approximately two disc diameters in size) involving the macular area. There was no change in the left eye. The patient was given Premarin (20 mg.) intravenously, and was advised to avoid rubbing the eyes and to continue his previous program. He received another injection of Premarin the following day. By December 17, 1959, there had been a dramatic improvement in vision. There was unequivocal evidence of absorption of the hemorrhages. By the following day, the patient volunteered that he also had noted significant improvement in the vision of the *left* eye, particularly in the course of driving and reading. His vision without glasses was 20/50 (right eye) and 20/70 (left eye).

In an attempt to prevent further retinal bleeding, the patient was given Premarin orally, the initial dosage being 0.6 mg. daily. This was followed promptly by increased dyspnea and peripheral edema—an effect largely attributable to the estrogen. Another attempt subsequently was made to administer Premarin orally, using a dosage of 0.3 mg. daily; the same idiosyncracy was evident, however. Over the ensuing month, he was given several intravenous injections of Premarin without incident. Resorption of the retinal hemorrhages continued during this time. No subsequent episodes of retinal bleeding were noted over the next several months, during which time further measures were instituted for treatment of the anascarca; these included complete bed rest, rigid restriction of sodium, and the administration of diuretics, aminophylline and an aldosterone-blocking agent (Aldactone).

Improvement in vision during estrogen therapy; ocular bleeding and reduction of vision upon withdrawal of estrogen

Case 4. E. L., a 65-year-old housewife with longstanding diabetes first was seen in consultation on January 11, 1960, at which time she was taking 60 units of protamine zinc insulin and 1.0 Gm. of tolbutamide (Orinase) daily. She had been having hypoglycemic reactions in the early morning, in association with definitely disturbed vision. In December 1958, a "blood clot" had developed in the left eye, following which her vision continued to deteriorate. She had been treated with bioflavonoids (C.V.P.) by an ophthalmologist, without benefit. There was symptomatic evidence of neuropathy in her feet and lower legs. She had been taking digitalis since an attack of heart failure. Partial hysterectomy had been performed many years previously; the ovaries were not removed. She was smoking half a package of cigarettes daily.

Examination of the eyes revealed moderate sclerosis of the fundal arterioles and widening of the veins. Several micro-aneurysms were present, but no overt hemorrhages or exudates. Vision in each eye was 20/100 (corrected). The rest of the physical findings were not remarkable except for marked diminution of the vibratory sense from the knees down.

The diabetic regimen was altered, with a shift to NPH insulin, adjustment of the diet,

and administration of other supportive medication (including vitamin B_{12} parenterally and vitamins orally). Tolbutamide subsequently was discontinued. Premarin was started orally (0.3 mg. daily) and was also given intravenously every two weeks (long interval due to the great distance traveled per visit). During this time the patient improved generally, but she was particularly impressed by the progressive improvement in visual clarity. She commented that previously she could barely make out the large headlines, whereas now she could read some fine print. On February 2, 1960, her vision was 20/70 in the right eye.

Following an attack of influenza, hypoglycemia developed. Her fasting blood sugar level was 60 mg. per 100 ml. At this time, her vision was 20/100 in the right eye and 20/200 in the left eye. The dosage of NPH insulin was reduced to 50 units daily, but she continued her other medication. Slight subjective improvement in vision occurred. A subsequent increase in the amount of insulin was necessitated by the excessive rise in her blood sugar level but it was well tolerated.

Thereafter, the patient experienced vaginal bleeding, which was unexpected in view of the history of hysterectomy. Estrogens were discontinued. Cytologic examination of the vaginal smear did not reveal any cancer cells. After six weeks without estrogen, the patient became despondent over the definite deterioration of her vision. When seen on May 16, 1960, approximately two months after discontinuing Premarin (oral), she stated that for several days she had noticed bleeding into her right eye again, with increasing loss of vision in that eye. Examination revealed a fresh hemorrhage in the superior disc, slightly more than one disc diameter in size. Vision was 20/200 in the right eye. The Premarin was started (0.3 mg. orally, five days a week) and she was also given Premarin intravenously. The previous diabetic program was continued, the only modification being the addition of one DBI tablet daily because of a blood sugar level consistently in excess of 200 mg. per 100 ml. Two weeks later, there was definite resorption of the hemorrhage, and no new hemorrhages were noted. The fasting blood sugar level was 109 mg. per 100 ml. Again she was given Premarin intravenously and advised to increase the oral dosage to 0.3 mg. daily. Three weeks later there was complete resorption of the recent hemorrhage.

Improvement in vision during estrogen therapy; relapse during placebo therapy

Case 5. *L. M.*, a 73-year-old white movie projectionist, had been treated since 1957 for pulmonary fibrosis, cor pulmonale, and mild cardiac failure. With a regimen consisting of rest, restriction of sodium, administration of digitalis, a diuretic (Diamox), vitamin B_{12} parenterally and other supportive medication, there was considerable improvement in the cardio-pulmonary status in the ensuing several months. For the next three years, there was no clinically significant deterioration in function of the heart or lungs.

During 1958 and 1959, the patient became increasingly incapacitated from working at his trade as a professional movie projectionist, owing to increasing difficulty in vision. In an attempt to improve his distant vision he went to the extreme of using field binoculars, but this proved of no avail and he was forced to retire. The patient was seen by two ophthalmologists, who found bilateral macular degeneration and diabetic-type exudates. His best corrected vision was 20/50 in the right eye and 20/40 in the left eye. A standard glucose tolerance test yielded the following blood sugar value: fasting, 129 mg.; one hour, 193 mg.; two hours, 153 mg.; and three hours, 124 mg. per 100 ml. The family history included two sisters with diabetes mellitus.

On September 24, 1959, Premarin was started orally (0.625 mg. daily) without any other modification of the program. He also was given Premarin intravenously, but was not told that visual improvement might occur. At the next visit, he volunteered that for several days following the injection he had been able to read the newspaper for the first time in several years without his magnifying glass. After approximately fifteen days, however, his vision regressed. The dosage of Premarin was increased to 1.25 mg. daily by mouth, and he was given weekly injections of Premarin intravenously. Once again, he commented that his vision had improved within several days, so that it was as good as it had been in many

years. For example, he cited his ability to read small print in the newspaper and in magazines in spite of page glare. He was able to distinguish clearly the fine horizontal stripes in neckties—a visual feat he had been unable to attain for a long time. By January 15, 1960, his vision had improved so much that he was able to resume work as a movie projectionist without experiencing difficulty in focusing upon the screen. At that time, his vision was 20/30 in the right eye and 20/40 in the left (with glasses).

On January 21, 1960, he was given identical-appearing placebo tablets to replace the previous estrogen tablets; the change in contents was unknown to him. At the time of his visit two weeks later, he stated that he had felt somewhat weaker generally, particularly in the lower limbs, but that his vision was virtually the same. He had 20/40 vision in both eyes. During his subsequent visit two weeks later, however, the patient stated that he had suffered an acute lapse of distant vision and that he could no longer clearly focus upon the screen. Another sign of this impaired vision was the fuzzy appearance of distant trees that had been clear before. The weakness of the lower limbs increased. The patient's close vision had changed only slightly, however, and vision measured 20/40 in each eye.

In order that this patient might remain in his job, he again was given Premarin orally (1.25 mg. daily), supplemented by an intravenous injection weekly. Within another week, there had been a significant improvement in the clarity of his vision by the criteria mentioned; this was corroborated by the ophthalmologist. His vision was recorded as 20/30 in the right eye and 20/40 in the left eye. During the first ten months of treatment, there was no significant change in the retinopathy or macular degeneration, ophthalmoscopically. However, on October 27, 1960—thirteen months after the institution of estrogen therapy—definite regression or disappearance of at least four fundal exudates was noted both by the author and the consulting ophthalmologist. At that time, the patient volunteered that his vision was better than it had been in many years. For the previous six months, the dose of Premarin had been reduced to 0.3 mg. daily, to obviate the gynecomastia caused by 1.25 mg. daily.

Preservation of impaired vision in a remaining eye during estrogen therapy; relapse after withdrawal of estrogen

Case 6. H. L., a 61-year-old housewife, had been known to have diabetes for approximately nine years. She was experiencing progressive difficulty with vision. In 1954 a right iridectomy had been performed, following which she lost virtually all vision in that eye. In 1955, an iridectomy was performed on the left eye. In July 1959, following poor control of her diabetes, there was progressive deterioration of the remaining vision in the left eye. Examination of the eyes revealed extensive micro-aneurysms of both retinae with extensive bilateral macular hemorrhages and degeneration.

The therapeutic program consisted of a diabetic diet, several daily snacks to prevent insulin reactions, 45 units of NPH insulin daily, vitamin B_{12} parenterally every second day, and other supportive measures. Because of continued deterioration of her vision, however, Premarin was given orally (0.3 mg. daily) for approximately one month. During this time, there was no appreciable change in her vision subjectively. The dose of estrogen was then increased to 1.25 mg. daily and, in addition, she was given Premarin intravenously. When seen one week later, the patient stated that for several days she had been able to read the fine print in a recent letter—something she had been unable to do for six months. This improvement lasted for a few days. Premarin (oral) was continued until December 8, 1959, when menstrual cramps and vaginal bleeding recurred for the first time in many years. The estrogen preparation was discontinued. Pelvic examination and cervical cytologic studies did not reveal any abnormalities. Premarin was given intravenously for several weeks, during which time the vaginal bleeding abated. She volunteered that no further bleeding ("ink spots") in the left eye had been noticed. Vision in her left eye was 20/50 on January 5, 1960.

Thereafter, the patient received no estrogen therapy for one month. At the time of the next visit, she stated that her remaining vision had deteriorated rapidly over the preceding few weeks. Among her criteria of vision, she used the ability to see the kitchen clock and other objects. Vision in her left eye was 20/70, and on a subsequent visit it was 20/100. The corresponding fasting blood sugar levels were 172 mg. and 182 mg. per 100 ml. The dosage of NPH insulin was increased to 50 units daily. In view of the continued deterioration, Premarin was resumed in intermittent small oral doses, and also intravenously once weekly. Anti-inflammatory enzyme (Chymoral) was given in a dosage of 1 tablet three times daily for two weeks. Only slight subjective visual improvement had been noted at the time of her visit three months later. The patient, nevertheless, was grateful for her minimal remaining vision and for the halt in the progression of visual failure. For this reason, placebo therapy was withheld.

During the ensuing year, while receiving Premarin orally (1.25 mg. three times weekly), the patient noticed a definite return of vision in her *right* eye. On several recent consecutive visits, vision in the right eye has been 20/100. She volunteered that she can clearly see the kitchen clock at a distance of 10 feet, and can now read newsprint with the aid of a magnifying glass—neither of which functions she can perform with the left eye. During May 1961, a trial course of nandrolone propionate (Durabolin)[3] was given in a dosage of 25 mg. intramuscularly once weekly (without Premarin), but there was no change in her status. Although the chronic perimacular chorioretinopathy in the right eye was unchanged, that eye remained singularly free of recent hemorrhage. Pressure in the left eye was found to be elevated at that time, and standard topical therapy was started by the attending ophthalmologist.

Improvement of vision during estrogen therapy; relapse after withdrawal; remission on resumption of estrogen therapy

Case 7. M. W., a 73-year-old colored female had been known to have diabetes for severa years. When first seen on April 21, 1960, signs of extensive polyneuropathy were present, particularly in the lower limbs. Other salient clinical features included: virtual absence of vision in the left eye; 20/200 vision in the right eye; micro-aneurysms, but no recent retinal bleeding or exudates; arteriosclerotic heart disease; and arteriosclerotic peripheral vascular disease with the Leriche syndrome. The initial blood sugar level was 417 mg. per 100 ml. This was accompanied by glycosuria without acetonuria, and a serum cholesterol level of 341 mg. per 100 ml.

A diabetic regimen was started consisting of an 1800-calorie diabetic diet, midafternoon and bedtime snacks, DBI, digitalis, vitamins orally, and B_{12} parenterally. DBI proved ineffective in controlling the diabetes, so it was replaced with NPH insulin in fractional doses. Owing to her domestic circumstances, she subsequently received only one injection of insulin daily. After several months of observation, it was found that 55 units of NPH insulin daily appeared to control the diabetes without incurring hypoglycemic episodes.

With this program, her general appearance and the neuropathy improved greatly. After several months, however, her already limited vision in the one functioning eye progressively deteriorated. She was given an intravenous injection of Premarin on a trial basis. At the time of her return visit one week later, she volunteered that her vision had definitely improved, but only for a few days. On June 1, 1960, Premarin (0.3 mg. daily) was started orally. The vision in the right eye improved from 20/200 to 20/40 to 20/30 over the ensuing two months, accompanied by striking subjective improvement in sight.

She then fared well until August 29, 1960, when slight vaginal bleeding occurred. The hormone was discontinued. Subsequent pelvic examination and cytologic study of the cervical secretions did not reveal any abnormalities. Ten days after estrogen had been stopped, she again began to experience increasing visual difficulty; visual tests showed

[3] Kindly supplied by Organon Inc., Orange, New Jersey.

progressive deterioration in the ensuing month. Three weeks later, Premarin was readministered orally in a dosage of 0.3 mg. on Mondays, Wednesdays and Fridays. When seen three weeks later, the patient volunteered that her vision had improved remarkably. No further vaginal bleeding occurred over the next four months, during which time her vision continued to improve both subjectively and objectively.

PATHOGENESIS OF DIABETIC RETINOPATHY: A REVIEW

Several aspects of the pathology and pathogenesis of diabetic retinopathy merit brief review in orienting clinicians to the problems involved, the rational of the described program of prophylaxis, and the possible modes of action of estrogens.

The earliest demonstrable *retinal changes* in the diabetic without arteriosclerosis, hypertension or renal complications take place in the veins. The veins appear dark and full; later they become tortuous and beaded, with perivascular sheathing. Back pressure to the venous capillary system by such venous stasis is most intense in this area of the vascular bed. This partly accounts for the characteristic *venous micro-aneurysms* and the predisposition to thrombosis of the central vein or one of its branches. The tendency for exudates to cluster around aneurysms indicates that the exudates may originate from leakage of plasma through the aneurysmal wall. Since micro-aneurysms are not found elsewhere in the eye or in other vessels (including those of the brain and serous membranes) their confinement to the retina probably is related to the venous stasis and the peculiar structure of the retinal capillary network. Ashton (31, 32) has suggested that the underlying mechanism is suboxidation and subnutrition of the vessel walls brought about either by a failure of the blood supply or by stasis of the venous circulation.

Although the micro-aneurysms of diabetic retinopathy generally are regarded as permanent changes, several observers have reported their disappearance (7, 16). As noted previously, this regression in some cases is related to disease or ablation of the pituitary or adrenals.

A vascular lesion characterized by endothelial proliferation and deposition of a network of PAS-positive, colloidal iron-negative fibrils has been noted with significant frequency in the venules and small arteries of the retina in diabetics (33). This lesion is similar to those noted in the vessels of the placenta, heart, kidneys and lower extremities. Unfortunately, detailed study of the retinal vessels is curtailed by the optical limitations of magnification. (This may be overcome ultimately by the use of scanning microspectrophotometry.)

The studies by Ditzel and his associates (34, 35) on the microvascular system in patients with diabetes mellitus, employing the bulbar conjunctiva method, demonstrate that a characteristic *abnormal vascular pattern* does exist, namely, tortuosity and elongation of the capillaries, narrowing of the arterioles, dilatation of the venules, and perivascular exudation leading to "hyaline" infiltration. Since the venular distention and increased permeability are maintained for long periods—even when intravascular aggregation of erythrocytes is minimal—this vascular abnormality tends to increase with duration of the diabetes. The

ophthalmoscope cannot disclose changes in the caliber of the terminal arterioles and smaller venules in a manner comparable to that in which the stereo-binocular microscope reveals such changes in the bulbar conjunctiva, but it can effectively demonstrate a disturbance of the arteriolar-venous ratio.

"Hemorrhages" that are well defined by ophthalmoscopic examination are virtually all micro-aneurysms. Irregular *hemorrhages* probably occur either by diapedesis through the aneurysmal wall or by rupture of the capillary aneurysm. These may take the form of large retinal hemorrhages, preretinal hemorrhages, or massive extravasations of blood into the vitreous (36). Retinal hemorrhages seldom occur in juvenile diabetics before micro-aneurysms are demonstrable, but they frequently are seen in older diabetics in the absence of micro-aneurysms (37).

Both the preretinal and vitreous hemorrhages in diabetics may precede or follow a proliferative phase which may suddenly develop after heavy work or a slight infection (37). The first vitreous hemorrhage may be absorbed relatively quickly (*i.e.*, in the course of several weeks) with the return of a significant degree of visual function (38). On the other hand, the rate of absorption becomes progressively slower with recurrent bleeding. Proliferative retinopathy, painful secondary glaucoma, and blindness may ensue under these circumstances if the process is left unchecked.

Retinitis proliferans, characterized by proliferating white fibrous bands extending across the retina or floating in the vitreous, probably represents a reaction to repeated large hemorrhages in most instances. It may occur as the result of repeated retinal hemorrhage from any cause (7). There is great variation in the time interval between the appearance of the first retinal hemorrhages and the development of the proliferative phase—usually at least two years (1). The characteristic neovascularization of the retina is found most commonly in patients in whom diabetes developed before the age of 40 years. When patients with and without proliferative retinopathy are compared, neither sex nor heredity appears to exert a significant influence (39).

Since the metabolism of the retina is unique—it has the highest rate of respiration of any tissue and a higher rate of glycolysis in air than most other tissues—it has been postulated that a vaso-formative factor is elaborated by the hypoxic retinal tissue and is inadequately removed owing to the concomitant vascular changes (32). This factor subsequently seeps into the vitreous, where the accumulation of a sufficient concentration serves to stimulate the formation of new vessels.

Diabetic retinopathy generally precedes the renal changes and can exist without intercapillary glomerulosclerosis (32). On the other hand, eye changes are usually demonstrable when there is nephropathy. In the experience of the Joslin group (1), albuminuria and hypertension were absent at the time of development of retinitis proliferans in one-third of the patients; subsequently, they remained absent for periods varying from a few months to several years. The resemblance of the thickened walls of retinal capillary aneurysms to the hyaline in the Kimmelstiel-Wilson nodule, and the production of these nodular lesions

in the dog kidney by cortisone and anterior pituitary extract are noteworthy (40, 41). The renal lesions are found predominantly on the arterial side, but the retinal lesions occur chiefly on the venous side.

The sclerosis and capillary fragility, which tend to increase with age, undoubtedly play a significant role in the genesis of the macular changes and the decreased vision. However, diabetic optic neuritis is relatively infrequent. The latter possibly represents a hastening and intensification of the vascular and neural degeneration, as well as increased susceptibility to the toxic effects of alcohol and tobacco (42). The gradual onset of the optic neuritis and the usual failure to improve are in contrast with the course of the relatively acute amblyopia stemming primarily from the use of tobacco and alcohol.

The observation that diabetic retinopathy and the Kimmelstiel-Wilson syndrome often first appear or become aggravated during pregnancy, infection, or the administration of corticotropin (states which tend to be associated with *increased adrenocortical activity*) also deserves mention (4, 27, 43). Becker has reported on the production of retinal lesions both in rabbits rendered diabetic with alloxan and in man following the injection of corticotropin (43). The latter clinical counterpart is distinctly unusual, however, considering the number of patients who have received steroids. A similar situation pertains in patients with Cushing's syndrome; diabetic retinopathy is rarely observed in these cases, in spite of the surplus secretion of "diabetogenic" hormones (9). Furthermore, attempts at reproduction of these lesions by the same investigator and by others have proven disappointing. It is possible that the adrenocortical changes are secondary phenomena, stemming from the prolonged stress and stimulation caused by frequent breaks in diabetic control, with repeated cycles of alternating hypoglycemia and hyperglycemia.

There is less evidence to indicate that *pituitary factors* are related to diabetic retinopathy, even though the pituitary adrenocorticotropic and growth hormones are known to exert a diabetogenic action (44). There even may be another specific pituitary factor which competes with insulin. No significant and constant structural change in the pituitary gland in diabetes has been demonstrated. Moreover, the incidence of diabetic retinopathy in patients with pituitary tumors who become diabetic does not appear to be increased. In one series of 66 patients with pituitary tumors, 30 had associated diabetes; only 2 of the 30 diabetics were found to have diabetic retinopathy (45).(Inasmuch as the majority of these patients who manifest pituitary diabetes tend to do so within the the first six years after clinical onset of the pituitary tumor, the infrequency of diabetic retinopathy in this situation may be related to a time factor.) Dexamethasone in a dosage of 3.0 mg. daily for more than four months (administered in an attempt to suppress the anterior pituitary or adrenal) had no beneficial effect on the retinitis proliferans of diabetes mellitus (46).

It has been suggested that a major factor in the vascular degeneration in diabetes is the continual *disturbance of intracellular and extracellular osmotic relationships.* The frequent transitory refractive changes causing blurred vision probably represent variations in the index of refraction of the lens nucleus that

result from variations in salt retention and the osmotic interplay caused by rapid shifts in the concentration of blood sugar. There is a slow decline in *intraocular tension* associated with the hyperglycemia that follows insulin withdrawal (37). This is explainable in part by the fact that insulin accelerates the transport of glucose through the blood-aqueous barrier in the eye and possibly through the hyaloid membrane. Consequently, the relative lack of insulin during periods of hyperglycemia delays the penetration of glucose into the vitreous, but does not interfere with the exchange of water through the hyaloid membrane. This leads to a withdrawal of water in the direction of the more hypertonic blood. Conversely, a precipitous rise in intraocular tension can take place during insulin-induced hypoglycemia. These variations in intraocular pressure undoubtedly influence the development of retinal-vein fullness, micro-aneurysms, and retinal hemorrhages from the vessel walls which are weakened by the diabetic angiopathy.

The complications of diabetes in man—in the absence of ketosis or acidosis—may be associated with, or influenced by, well-defined *changes in the pattern of serum lipids and the serum and tissue polysaccharides.* Adlersberg (47 *a*) and others have stated that elevated levels of these serum components might be related pathogenetically to the development of diabetic retinopathy and glomerulosclerosis. Adlersberg (47 *a*) compared the sera of a group of diabetic patients with early retinopathy but no renal involvement, to the sera of patients with uncomplicated diabetes and those without diabetes. He found significant differences. In the diabetics with retinopathy, there was an increase in the serum levels of triglycerides, total lipids, glucosamine and total polysaccharides, while the levels of cholesterol and phospholipid were normal. These blood changes may precede the degenerative alterations of the tissues and the deposition of certain protein-lipid and protein-carbohydrate components in the retina and in the renal glomerulus.

One of the earliest histologic manifestations in the retina is the deposition of lipid material in the wall of the capillaries between the layers of the PAS-positive basement membrane. This is followed by progressive ballooning and formation of aneurysms. In advanced diabetic retinopathy, there is a free and perivascular deposition of cholesterol crystals and lipid (7, 47 *b*). The stabilization of such relationships may result from the changes in the levels of blood sugar and serum lipids brought about by the use of *estrogens*, *heparin* or other agents (45, 48). This offers another explanation for their salutary effect in diabetic retinopathy, as discussed in the next section.

Interest also is increasing relative to the possibility of an underlying *immune phenomenon* in the pathogenesis of certain diabetic complications. This is based upon the presence of fibrinoid and other histologic changes, elevation of the alpha-2 globulin level (comparable to that observed in auto-immune reactions), and the glomerular lesions found by means of fluorescent tagged antibody staining technics (49).

HEMOSTATIC ACTION OF ESTROGENS

Estrogens have proved of value as hemostatic agents—particularly when administered intravenously—for the control of epistaxis in hemorrhagic telangiectasia, hemoptysis in pulmonary tuberculosis, delayed post-traumatic hemorrhage, corticosteroid-induced ecchymoses, anticoagulant-induced bleeding, functional uterine bleeding, massive gastro-intestinal hemorrhage associated with cirrhosis, and the bleeding following tonsillectomy, prostatectomy or ophthalmic surgery. (18, 19, 50–57) As far back as 1933, it was shown that abnormal bleeding times in newborn infants could be lowered by administration of crystallized estrin (Theelin) parenterally (58). The case is on record of an elderly hemophiliac in whom massive hemorrhage following dental extraction had been uncontrollable until the administration of estrogens (Premarin) intravenously (59).

A rapid increase in the concentration of estrogens is probably an essential factor in promoting coagulation of the blood in cases of hemorrhage; this might explain the absence of such a hemostatic effect with continued oral administration (60). The clinical application and pharmacologic basis of the hemostatic activity of estrogen currently are under study by several investigators besides the author. It appears that conjugated estrogens exert a limited influence on various links in the blood clotting mechanism but, more significantly, in and around the vascular bed.

Johnson (61) observed a sharp *rise in Factor V* (plasma Ac-globulin) and *prothrombin concentration* following the intravenous infusion of estrogenic hormones into dogs. These changes were noted within the first fifteen minutes and reached a peak in approximately ninety minutes; by four hours, however, the concentrations of both Factor V and prothrombin were within normal limits. Detailed studies in humans relating specifically to the effect of intravenous injection of Premarin on the individual factors involved in the coagulation process have recently been made (62). The increase in Factor V was confirmed, but no demonstrable changes in the prothrombin time, the prothrombin content, Factor VII, the bleeding time, the clotting time or clot retraction could be found in these studies or by the author (18).

The rise in concentration of Factor V following administration of estrogen merits further comment. The values for this factor normally tend to be high in the dog, whereas in the human they are among the lowest (10–15 units per ml.) for all the species that have been tested (63). Accordingly, a depression of but a few units in man might have an important bearing upon the course of bleeding in certain instances (61). Conversely, any agent that can effect an elevation in the level of Factor V could possibly prevent or control bleeding.

A decrease in the antithrombin activity of plasma following intravenous administration of estrogen has also been noted (61). Such an action might increase the amount of available thrombin, enhancing coagulability of the blood. Others have observed similar changes in antithrombinic activity following the administration of synthetic estrogens. A related observation concerns the effect

of intravenous injection of Premarin upon abnormalities of the coagulation mechanism in dogs subjected to acute radiation. Following injection of the estrogen, a definite increase was observed in the prolonged clotting time so induced—between thirty minutes and one hour. As in the case of the studies previously cited, however, this influence was short-lived (64).

The *inhibition of fibrinolytic activity* by estrogens is reflected in the rise of blood fibrinogen levels (65). Intravenous administration of estrogens has proved effective in the management of fibrinolysis during and after surgical operations, particularly those on the prostate (66).

Estrogens exert an appreciable *effect on the capillary bed*, a conclusion supported by several clinical observations. For example, recurrent epistaxis in hemorrhagic telangiectasia is suppressed both cyclically in relationship to the menses and following the oral administration of estrogens (54, 55, 67). With the use of estrogens, the author repeatedly has been able to suppress and prevent bleeding from the mucous membranes and bleeding into the skin induced in susceptible patients by anticoagulants or by prolonged treatment with large doses of the adrenocortical steroids (18, 19). In a patient having severe thrombocytopenia due to aplasia of the marrow, widespread hemorrhages into the skin and virtually all the mucous membranes were minimized, and prevented from recurring over a period of more than four months, by the use of Premarin intravenously (20 mg. once to thrice daily); previous treatment with large doses of dexamethasone, vitamin C, vitamin K, bioflavonoids, and multiple transfusions of fresh blood had proved ineffective. Furthermore, it was possible to perform three aspirations of bone marrow without complications under this pharmacologic "umbrella," at a time when the platelet count was 11,000 per cu. mm., the bleeding time over twenty minutes, and clot retraction almost nil at three hours.

Perhaps the most significant studies explaining the clinical hemostatic action of estrogens are those dealing with their *effect on tissue mucopolysaccharides.*

Ground substance is composed chiefly of acid mucopolysaccharides (hyaluronic acid, and chondroitin sulfate A, B and C) and proteins. A mixture of acid mucopolysaccharides constitutes the cement substance of capillaries, and the capillary sheath is composed solely of hyaluronic acid. The ground substance is in sol-gel equilibrium dependent upon the polymerization and size of the mucopolysaccharides, *i.e.*, the shorter the polysaccharide molecule, the greater the solution state (sol) of the ground substance. Conversely, the longer the molecule, the firmer (gel) the ground substance.

It is pertinent that the mucopolysaccharides comprising the ground substance of blood vessels display significant anticoagulant properties which can be neutralized with protamine—particularly the chondroitin sulfate B component (51). Furthermore, this material stimulates the production of a lipid-clearing factor when injected intravenously into rats. The more deeply lying constituents of the vessel wall—as well as the intact endothelium—may play an important role in maintaining the normal fluidity of blood, and focal depletion of the acid mucopolysaccharides of vessels may represent a significant basis for the propensity to thrombosis-formation in atherosclerosis.

By means of the colloidal iron stain (with which collagen stains red and acid mucopolysaccharides blue) and the toluidine blue stain (in which metachromasia increases with the length of the polymer), Schiff and Burn (68) repeatedly demonstrated a progressive change from the sol state to the gel state of the tissue mucopolysaccharides in hamsters, monkeys and man that lasts several hours following the intravenous injection of conjugated estrogens. This alteration in the ground substance about the small blood vessels and in the arteriolar walls appears to be due to an increase both in the quantity and polymerization of the mucopolysaccharides; it occurs equally in males and females. Preliminary observations by the same investigators (69) indicate that the adrenocortical steroids favor a change in the reverse direction, *i.e.*, to the sol state.

The intravenous injection of conjugated estrogens induces an increase in the level of serum hyaluronic acid (62). It also causes delay in the absorption time of intradermal hyaluronidase wheals (62).

Estrogen may act on the ground substance in the form of a metabolite rather than as a specific endocrine. Schiff and Burn (68) speculated that the action might take place through stimulation of the production of glucuronic acid, which enhances the synthesis of mucopolysaccharides (since this substance is an integral part of both the hyaluronic and the chondroitin sulfate molecule).

Other possible hemostatic mechanisms of estrogen therapy include a serotonin-like action and the neutralization of a vascular toxin (70).

OTHER PERTINENT METABOLIC AND ENDOCRINE EFFECTS OF ESTROGENS

Estrogen therapy is not generally considered to influence the underlying diabetic state significantly. From a clinical standpoint, however, the author harbors the impression that, as adjuvant therapy in certain female diabetics with serious retinopathy, neuropathy and other complications, administration of estrogens tends to reduce and stabilize insulin requirements and to minimize the incidence of alternating episodes of hypoglycemia and ketosis. There is a decided decrease in the insulin requirement post partum in diabetics who have received large doses of estrogen during pregnancy (1). Similar observations in the nonpregnant diabetic female have been made by others since Mazer pointed out that estrogens can cause an appreciable decrease in the sugar content of the blood and urine in diabetic women (71, 72). Supportive estrogen therapy in the diabetic—aside from its emergency use in intraocular bleeding—appears to be most helpful when the onset of the diabetes coincides with the menopause, or when diabetes is present in patients of any age group demonstrating signs of hypo-ovarianism.

Some of the improvement in diabetic retinopathy reported here may be related to an *effect upon lipid content* as well as the vascular pathology. It has been reported that administration of lipotropic factor can prevent disseminated hemorrhages in the fundus of pancreatectomized dogs receiving insulin (73) and can modify diabetic retinopathy in the human subject (8). The reported salutary effect of sublingual administration of heparin upon diabetic retinopathy also is predicated upon its "clearing" effect on elevated serum lipid levels.

A striking decrease in serum lipid content can be produced by prolonged estrogen therapy, without any dietary lipid modification, in both males and postmenopausal females with myocardial infarction (74, 75). This "normalizing" effect on the serum cholesterol and phospholipid concentration tends to be maximal and maintained after ninety days of therapy. Little difference is noted between ethinyl estradiol, Manvene and Premarin in this regard, except for fewer side-effects with the latter (74). Prolonged administration of estrogen does not appear to be associated either with diminution of the metabolic effect, acquisition of tolerance, or resistance to the hormone (17). In a large number of postmenopausal women receiving long-term therapy with conjugated equine estrogens for cardiovascular disease, the optimal dosage to insure lowering of the serum lipid level with minimal side-effects was 1.25 mg. daily when the uterus was intact, and up to 2.5 mg. (if tolerated) in women previously subjected to a hysterectomy (74). In patients observed at least one year, "breakthrough" uterine bleeding occurred in 2 of 13 women receiving a dosage of 0.625 mg. daily and in 4 of 19 receiving 1.25 mg. (A dose of 0.625 mg. of Premarin is estimated to be the equivalent of 0.02–0.05 mg. of ethinyl estradiol.) Marmorston and her colleagues (76) have demonstrated that significant reduction in the serum cholesterol level and the cholesterol/phospholipid ratio can be achieved in male patients with myocardial infarction who are given daily doses of estrogen so moderate that there is no development of breast tenderness. Gitman and Greenblatt (77) reported diminution in the serum concentration of beta lipoproteins of the S_f 12–20 and 20–100 classes following a single intravenous dose of Premarin in a patient with coronary insufficiency. Relatively small doses of methyltestosterone can counteract completely these biochemical effects of estrogens when the two are administered simultaneously (17).

In addition to the marked reduction in serum lipid and lipoprotein values, striking disappearance of xanthomatous lesions has been induced by means of oral estrogen therapy in patients with primary hypercholesterolemic xanthomatosis and idiopathic hyperlipemia (17, 78).

Interest has been redirected recently to the observation that estrogens can stimulate *the phagocytic activity of reticulo-endothelial cells*—a mechanism that probably plays an important role in cholesterol metabolism (79). This could explain, for example, the enhanced resolution of local subcutaneous implants of absorbable gelatin sponge saturated with cholesterol, without detectable alterations in the level of serum cholesterol (80). Similarly, administration of diethylstilbestrol can completely arrest the progress of pre-established atherosclerosis of the aorta induced by cholesterol feeding in rabbits, even though the hypercholesterolemia is not influenced (81). The potential for such an estrogenic influence on human and experimental coronary atherosclerosis (namely, local alterations in the coronary vessels being effected without demonstrable changes in the serum cholesterol level, phospholipid/cholesterol ratio or the lipoprotein pattern) is already demanding the attention of clinicians. Impressive improvement has been reported (75) in the mortality of patients with previous myocardial infarction who were treated with estrogens orally for prolonged periods;

the enhanced survival rate could not be correlated with the effect on serum lipids, however. It is also pertinent that the exudative lesions in and about the macular areas contain macrophages laden with lipid material (47 *b*).

In this study, the possibility was entertained that osmotic changes in the vitreous induced by estrogens (either orally or intravenously) caused the relatively prompt objective improvement in the vision of several patients, since these changes could counteract those created by swings in the blood sugar level. A survey of the indexed medical literature by a librarian of the American Medical Association, however, failed to uncover basic pertinent data (82).

Hench (83) has speculated upon the important clinical and pathogenetic potentialities of major cortisone "ebb-tides" as related to the onset, exacerbation and recurrence of certain rheumatic and collagen inflammations. Similarly, there are important *estrogen "ebb-tides"* which may be related to the pathogenesis of various spontaneous and cyclic hemorrhagic manifestations. Clinical examples include the increased tendency to bleeding from hereditary telangiectasia prior to the menstrual period, after the menopause, and following ovariectomy (67).

Estrogens act catalytically and in low concentration at a critical level of cell metabolism in a wide variety of tissues. For example, diethylstilbestrol strongly inhibits the diphosphopyridine nucleotide oxidation normally carried out by enzymes from a variety of mammalian tissues, tumors and micro-organisms. The site of this inhibition has been localized in skeletal muscles to DPNH cytochrome C reductase (84). Since the nucleotide specific electron transport pathways represent critical control points in metabolic reactions, this inhibitory effect shared both by estrogens and other hormonally active steroids enables small amounts to exert significant metabolic influences, even in tissues devoid of steroid enzymes.

Another interesting effect of estrogenic substances in catalytic oxidation has been observed in a study of their influence upon the transport of plasma copper and ceruloplasmin. The binding forces holding the 8 copper atoms of ceruloplasmin are divided into 4 that are held by relatively weak forces (readily removed by chelating agents such as versene), and 4 that are firmly bound. In both, the labile and stable copper atoms are associated with reactive sites capable of catalytic oxidation of catechol and other amines and serotonin. The labile copper atoms also are involved in catalyzing the oxidation of ascorbic acid. In both normal volunteers and in certain cancer patients, it was found that the ceruloplasmin content rose from two to eight times the normal level following administration of stilbestrol; the plasma values returned to their initial levels when the drug was discontinued (85).

Study of the retinal metabolic characteristics in normal and alloxan-diabetic rats has indicated a lower rate of anaerobic glycolysis and a considerably greater oxygen consumption in the retinas of diabetic rats when sodium succinate was employed as the substrate (86). No such data are available as yet concerning the effect of estrogenic substances, but the response in tissues other than the retina has been studied. The metaphyses of estradiol-treated male mice *in vitro*

demonstrate a decrease in lactate production in air and an increase in glucose consumption under anaerobic conditions. Recently, this so-called Pasteur effect has been shown to be due to a direct action of the hormone on bone-cell metabolism (87). The addition of estradiol-17β *in vitro* increases oxygen consumption in the adenohypophysis (but not in the liver or kidneys) both in man and the rat (88).

The experimental and clinical evidence that development of diabetic retinopathy is associated with—and possibly pathogenetically related to—adrenocortical hyperfunction was cited previously (4, 27, 43). It has been postulated that hypophysectomy might be of benefit because it checks adrenocortical hyperfunction and specifically prevents the elaboration of diabetogenic pituitary somatotropin (89). "Medical adrenalectomy" or "medical hypophysectomy" has been attempted with testosterone, progesterone, or pituitary radiation (9). As previously noted, the beneficial effects of hypophyseal stalk section have been attributed to an effect upon some humoral factor elaborated by the pituitary or hypothalamus (16 *b*).

Therapy with estrogenic hormones also may serve to *modify the function both of the adrenals and the anterior pituitary*, and in this manner influence the course of diabetic retinopathy. The increase in oxygen consumption in the pituitary after the *in vitro* addition of estradiol-17β has been already mentioned (88). The following clinical observations indicate that secretion of growth hormone by the pituitary can be depressed by estrogens, particularly in acromegaly: 1) Albright has presented evidence suggesting that large doses of estrogens (15 mg. of diethylstilbestrol daily) exert a suppressive effect in some cases of acromegaly; 2) McCullagh has reported disappearance of diabetes in acromegalics during treatment with estrogens; and 3) Hurxthal *et al.* (90) have noted that there may be a decrease in the level of blood phosphorus following estrogen administration. However, the possibility of increasing the size of a pituitary adenoma by estrogen therapy and thus causing further visual deterioration must be born in mind (90, 91). Although proof is not as yet available, data showing that estrogens can depress growth hormone secretion may be forthcoming with the development of sensitive methods for measuring growth hormone levels in serum (92, 93).

Recently strong evidence has been presented to support the view that human growth hormone is diabetogenic, based upon the marked nitrogen and electrolyte retention, ketosis, and impairment of glucose tolerance in patients receiving the hormone for prolonged periods (94). This is pertinent to the fact that the onset of juvenile diabetes often is preceded by a period of abnormally rapid growth. The demonstration that the concentration of a growth-hormone-like factor is frequently elevated in the plasma of young diabetics (94 *b*) adds further credence to this tenet.

Clinical observations indicate that estrogens can inhibit synthesis of the corticosteroid hormones. An example is the striking disappearance of all evidences of Cushing's syndrome—along with normalization of the urinary 17-ketosteroid excretion and the eosinophil count—as noted by Kovacic (95) in a patient with probable adrenocortical hyperplasia who was treated with daily

doses of 5 mg. of diethylstilbestrol. Hydrocortisone is transformed to certain of its metabolites under the influence of estrogens. The daily administration of as little as 0.5 mg. of diethylstilbestrol orally is sufficient to produce an elevated concentration of plasma free 17-hydroxycorticoids (96). (The biologic activity represented by this dose is comparable to the amount of estradiol estimated to be secreted during the menstrual cycle.) Urinary corticoids are decreased from 30 to 50 per cent of the control levels after two or three weeks of estrogen administration in both males and females, representing a decrease in the rate of synthesis of cortisol and corticosterone (97). These increased levels of plasma free 17-hydroxycorticoids in patients receiving estrogen have been attributed to a change in steroidal distribution in which the tissue cortisol levels fail to rise to the same degree as the plasma levels, resulting in lack of sufficient response by the pituitary-adrenal feedback mechanism to restore the plasma 17-hydroxycorticoid levels to normal (96). Such an explanation is supported by the lack of Crooke's changes in the pituitary basophil cells in patients with carcinoma of the prostate receiving long-term estrogen therapy (96). This rise in the plasma level of hydrocortisone following estrogen therapy is *not* associated with a depression of the eosinophils (98). Prolonged administration of estrogen to non-acromegalic male and female patients has not resulted in the marked pituitary and adrenal enlargement or the pituitary tumors observed in the rat (91).

A competitive inhibition between cortisol and estrogens at an enzymatic level is likely since the defect in biotransformation can persist for weeks following discontinuance of the estrogen. This may involve either the level of one of the co-enzymes (TPNH) or of the TPNH-linked steroid dehydrogenases in the liver necessary for enzymatic inactivation of these steroids. For example, the predominant initial reaction in the metabolism of cortisone is a reduction of the C-11 ketone to an 11-hydroxyl function (cortisol).

Administration of estrogen in both men and women causes a rise in the protein-bound-iodine fraction of the serum due to augmentation of the iodine-binding capacity—an effect that is sustained during such treatment (99). There are no other clinical or laboratory evidences of increased thyroid function, however. Similarly, although the expected testicular depression accompanies these chemical changes in middle-aged men with coronary atherosclerosis, no apparent detriment to thyroid or adrenal function has been demonstrated with doses of equine conjugated estrogens averaging 10 mg. daily for periods exceeding one year (100).

PROPHYLACTIC CONSIDERATIONS

Another ocular condition involving diabetic patients, in which estrogenic substances may prove of considerable prophylactic value, relates to operation for the *extraction of cataracts.* Diabetics are particularly prone to hyphema, a frustrating and prolonged complication that can negate completely the benefits of the most meticulous surgery. The intravenous administration of estrogens approximately ninety minutes before surgery on the second eye can prevent such bleeding in diabetics who previously had suffered hyphema following extraction

of a cataract (101). Inasmuch as these individual patients act as their own controls, this observation is all the more impressive.

Initial estrogenization can control traumatic intraocular bleeding in animals subjected to iridectomy. Studies have been made in rabbits concerning the effect of Premarin intravenously on the bleeding resulting from injury to the extraocular soft tissues (102); a decreased loss of blood and a significant reduction in the bleeding time followed such treatment.

Proliferative retinopathy may be avoided by measures to prevent bleeding and hasten resorption of blood. The author believes that estrogens may do both, Final proof awaits the results of observations over a prolonged period, particularly in the presence of engorged retinal veins that indicate impending bleeding into the retina or vitreous chambers, or thrombosis formation.

Dramatic acceleration in the resorption of ocular hemorrhage has been reported in nondiabetic patients following intravenous injection of estrogens; postoperative hyphema has disappeared within four days (103). In Goldberg's (104) study, the intravenous injection of estrogens strikingly prevented secondary glaucoma and subsequent blindness following traumatic hyphema, namely, a 20 per cent incidence in a control group as compared with none in the treated group. A colleague (105) has observed striking regression of massive subconjunctival bleeding in 3 patients following several intravenous injections of estrogens, obviating the need for incision.

The enhanced resorption of hemorrhagic residues induced by estrogens may be explainable in part by an effect upon a spreading factor (68, 69). The inhibition of hyaluronidase wheals following the intravenous injection of estrogens indicates that estrogens act on the ground substance to limit the activity of hyaluronidase (62 *b*, 106). The greater response in male patients suggests a sex difference.

The association of retinitis proliferans with clinical diabetic nephropathy and premature atherosclerosis in the young patient with severe diabetes is impressive. In view of the aforementioned clinical, biochemical and pathologic evidences that the atherosclerotic process can be influenced favorably by estrogenic therapy, and the possibility that there is a common pathogenic influence, prolonged estrogen therapy supplementing adequate diabetic management prior to irreversible damage might prevent or favorably influence lesions both in the retina and kidneys. Such long-term studies already have been instituted. The chief difficulty encountered to date has been edema or aggravation of edema after oral administration of estrogens in diabetics having either advanced renal disease or myocardial disease.

The controversy continues as to whether the administration of estrogens in large doses, along with progesterone, from the sixth week of pregnancy until delivery can prevent the development of toxemia in the pregnant diabetic and significantly influence the fetal survival rate (107). Pregnant diabetic women with no diabetic retinopathy, or that of the nonproliferative type, usually bear living babies. Unfortunately, in pregnant diabetics with retinopathy of the proliferative type, even treatment with large amounts of estrogens and other

hormones cannot prevent damage to vision; the rarity of a live baby suggests that pregnancy is contraindicated. On the other hand, improvement has been observed post partum in the ocular lesions of patients whose retinopathy had advanced during pregnancy, so pregnancy need not be terminated for that reason (1). A pilot study of the effects of intermittent intravenous administration of estrogens in such patients is in order.

ADJUNCTIVE USE OF OTHER AGENTS

Other agents may be of value in the subsequent clearing of the hemorrhagic residues in cases of diabetic retinopathy, once the bleeding is controlled—notably the anti-inflammatory enzymes. Since the present effort was primarily an attempt to evaluate estrogen therapy in diabetic retinopathy with a limited number of patients, these drugs usually were withheld. On several occasions, however, they were used to advantage—for example, in Case 1.

Small doses of buccally administered proteases combine with salivary plasminogen to form plasminogen activator. The latter in turn presumably diffuses through the buccal mucosa in quantities sufficient to activate fibrin plasminogen into plasmin at the site of the acute tissue injury (108). Although streptokinase-streptodornase (Varidase, buccal) contains carbohydrate (and on occasion has rendered the diabetic patient more hyperglycemic), any ocular benefits are apparent within a few days, following which the medication can be discontinued. The value of the buccal route has been questioned recently on the basis of double-blind studies (109).

Similarly, trypsin may be used by several routes to aid resorption of localized blood. This drug also acts as a proteolytic and anti-inflammatory enzyme, aiding the host-induced control of localized inflammation and preventing excessive edema of the soft tissues. It does not inhibit or suppress formation of granulation tissue, as do the adrenal corticoids. Large doses of this agent (*i.e.*, 30 mg. daily) have been administered buccally to diabetics over a period of months without significant toxicity and with apparent amelioration of an associated nephrotic syndrome (110). Studies involving the supportive use of similar agents, including parenteral administration of chymotrypsin (Chymar, Aqueous)[2] and oral administration of chymotrypsin plus trypsin (Chymoral)[2] are in progress.

Heparin sublingually has been employed as a lipid-clearing agent in cases of diabetic retinopathy, with salutary effects (111). Along with a decrease in the serum chylomicron count, a diminution in the amount of exudative material around the macula and a disappearance of micro-aneurysms was observed following the administration of 1500 international units of crude heparin four times daily. We plan a trial study of the combined effect of heparin sublingually and estrogens orally in the treatment of diabetic retinopathy.

SUMMARY

An approach is presented to the management and prevention of intraocular hemorrhage by means of estrogens administered orally and intravenously in

patients with diabetic retinopathy, as a supplement to a described plan of conservative management. The rationale for such therapy is considered in relation to the difficulties inherent in such an evaluation.

The observations were made on 9 patients over relatively prolonged periods, judged in the light of either control data or data collected during periods of placebo administration. Seven illustrative case reports are presented.

Administration of estrogens intravenously may help prevent hyphema in diabetics being subjected to cataract surgery, particularly after previous troublesome intraocular hemorrhage.

There is additional evidence for the value of long-term estrogen therapy in preserving or improving vision in patients having diabetic retinopathy without bleeding. The case histories of 3 such patients are cited.

The possible modes of action of estrogens in the observed cases are discussed.

The possible potentiation of these estrogen effects by the use of other agents, such as the anti-inflammatory enzymes and heparin, deserves further study.

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Addendum

Following a preliminary report by the author of the use of estrogens in diabetic retinopathy (112), it was brought to his attention that significant ophthalmologic improvement has been observed in several European clinics in the course of prolonged studies with nandrolone phenpropionate (Durabolin, 25 mg. per week) and Deca-Durabolin (50 mg. every three weeks) (113, 114). Impressive improvement in both the vitreous hemorrhages and retinitis proliferans was observed in association with disappearance of some of the protein and fat abnormalities. It is likely that these agents and estrogens share a common pharmacologic effect. With the use of Durabolin and Deca-Durabolin, however, striking hypoglycemia has been observed; this in turn, was thought to induce or accentuate retinal bleeding in some instances.

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A NEW TABLET FORM OF CHLORAL HYDRATE (WM-1127) IN THE TREATMENT OF INSOMNIA IN THE AGED: DOUBLE-BLIND STUDY

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Insomnia is one of the most common complaints heard by the practicing physician, as attested to by the nation's annual expenditure of more than $100,000,000.00 for soporifics (1). Yet relatively little has been written about this subject, either in standard medical textbooks or in current medical literature. Even the physiology of sleep is not well understood, although significant research in this area has been started in the past few years.

The causes of insomnia are multiple. The most common psychic factors in the elderly are anxiety, worry or tension. Moreover, inadequate physical activity does not give rise to the fatigue conducive to sleep. Old people often take "cat-naps" and retire early in the evening; they become "slept-out", awaken early in the morning, and then complain of inability to sleep. Organic diseases, particularly those accompanied by pain, dyspnea or other discomfort lead to restlessness during the night. Thus the treatment of insomnia should be individualized, and a definite attempt made to determine and control the cause. Systemic disease should be appropriately treated, anxiety alleviated, and patients encouraged to get sufficient exercise during the day so that they will be reasonably tired at bedtime. Sedatives and hypnotics should be used only in cases in which insomnia cannot be controlled with conservative measures.

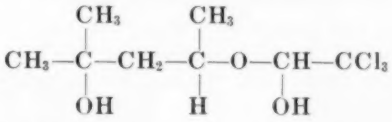
The geriatric patient presents a special problem when it comes to sleep disorders. Despite the almost complete absence of controlled studies, we frequently hear that barbiturates should not be given to the elderly, since they produce stimulation, confusion, excitement or other undesirable side-reactions. In a previous study (unpublished) we found that 17 per cent of patients past the age of 70 who were treated with secobarbital had reactions of this type, and we concluded that the effects of short-acting barbiturates are, indeed, unpredictable. The choice of a sedative for the geriatric patient is therefore not as easy as for the younger person. Many of the new synthetic preparations, however, have been used with success, and have a definite place in modern medicine.

Chloral Hydrate Combination

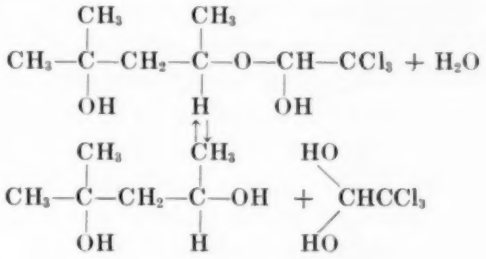
Chloral hydrate is by no means new, having been discovered by Leibig in 1832, and introduced as a hypnotic by Liebrich in 1869. It proved to be safe and effective, but fell into disuse about thirty years ago with the advent of the barbiturates. The main reason for discontinuing its use was the objectionable taste, which could not be disguised with even the most pleasant-tasting vehicles. A recent development, however, has allowed molecular linkage of chloral hydrate with hexylene glycol to produce a hypnotic in palatable tablet form (WM-1127). Hexylene glycol is a safe preparation which has been in use for several years. In

purified grade it is employed in the processing of foodstuffs, essences, perfumery and cosmetics, as well as medical products. In the medicinal tablet, it is only a means of carrying chloral hydrate and has no sedative action.

The new combination is 2-methyl-2,hydroxy-4-(2′,2′,2′-trichlor-1′-hydroxyethoxy)pentane with the following structural formula:



This compound is a hemiacetal combination of chloral hydrate and 2-methylpentane-2,4-diol which, under the influence of water, is slowly hydrolyzed into its components. The process is an equilibrium reaction:



Background of Study

The Methodist Home for the Aged in Philadelphia presents a typical cross-section of geriatric patients. At the present time there are 250 guests, ranging in age from 71 to 101. Only 25 are males. Although there are complete medical facilities, including a 72-bed geriatric hospital, this is no nursing or convalescent home. It is a place of residence for the aged person for the remainder of his life. Each resident is in good physical condition upon admission to the Home, but degenerative or neoplastic diseases may develop after admission. Since all guests are assured of good care and a place to live, the feelings of insecurity and worries about the future, so common in aged people, are minor. Except for these two factors, all of the anxieties and tensions common to a geriatric practice are found here. Despite good medical care, the use of tranquilizers and hypnotics is frequently necessary. We therefore became very interested in this new form of chloral hydrate and decided to evaluate it in a impartial manner. Since many fears and anxieties may be allayed just by giving a pill, the study was conducted by the double-blind method.

METHODS AND MATERIALS

The investigation was carried out on 56 geriatric patients, all of whom complained of inability to sleep. The youngest was 71 years of age and the oldest was 96. A total of 150 records were kept on the 56 patients, each record covering a 24-hour period. Two identical tablets were used, and they were given on a strictly alternating basis by the nurses on duty. One group of tablets was labeled "E-520" and the other "E-528"; this was the only detectable difference. In one group, each tablet contained 800 mg. of chloral hydrate-hexylene

glycol (500 mg. of active chloral hydrate); in the other group, each tablet contained placebo.

The tablets were given at a uniform time, usually 9:00 p.m. Each patient was examined every half hour by the physician on the service, who kept records regarding the presence or absence of sleep, restlessness, thrashing around, noisiness, and coherence. Any patient not asleep within thirty minutes was given a second tablet. On the following morning the same physician evaluated each patient for evidence of gastric irritation, headache, drowsiness, nervousness, visual disturbances, paresthesia, and any other indication of "hangover." Each patient's record was filed after adding the patient's own opinion of his sleep.

At the conclusion of the study the code was broken. We learned that "E-520" contained the chloral hydrate and "E-528" was the placebo.

RESULTS

Onset of sleep

Figure 1 is a summary of the data on the time interval between administration of the tablet and the onset of sleep, showing that 53.3 per cent of patients who received chloral hydrate were asleep within thirty minutes and 37.2 per cent of those who received placebo were asleep within this time. All who were not asleep within thirty minutes were given a second tablet similar to the first one. At the end of sixty minutes, the proportion of sleeping patients had risen to 81.3 and 54.5 per cent respectively. Within ninety minutes 87.9 per cent of the chloral hydrate group and 65.1 per cent of the placebo group were asleep. Since the onset of chloral hydrate sedation is considered to occur within ten to fifteen minutes (2), it appeared that the one-tablet dosage of this preparation was adequate for about half of the patients. The remaining 46.7 per cent required at least two tablets (1000 mg. of active chloral hydrate).

The psychogenic effect of placebo medication was well demonstrated. Many anxieties are relieved by suggestion, and there was a progressive trend in the number of patients falling asleep. In the placebo group, 37.3 per cent fell asleep promptly with one tablet; with a second placebo tablet the proportion increased to 65.1 per cent within ninety minutes.

Several of the patients in both the chloral hydrate and placebo groups were in the "no sleep" category at ninety minutes; later in the night they dropped off to sleep, but they were not listed in the effective categories for two reasons: 1) chloral hydrate is absorbed within thirty minutes and any sleep occurring after ninety minutes was probably not directly due to the sedative; and 2) it was impractical to check the patients throughout the whole night.

The difference between the effects of the two medications, however, was statistically significant.

Patient's opinion of sleep

Figure 2 represents the patients' opinions of the sleep obtained. The striking finding was that 97.4 per cent of those who received the active drug felt that sleep had been satisfactory, whereas only 56.0 per cent of those who received the placebo had a similar opinion. We have been unable to find a reference to any hypnotic preparation that is as effective as chloral hydrate; perhaps that is one reason why it has remained in vogue for such a long time. The findings are

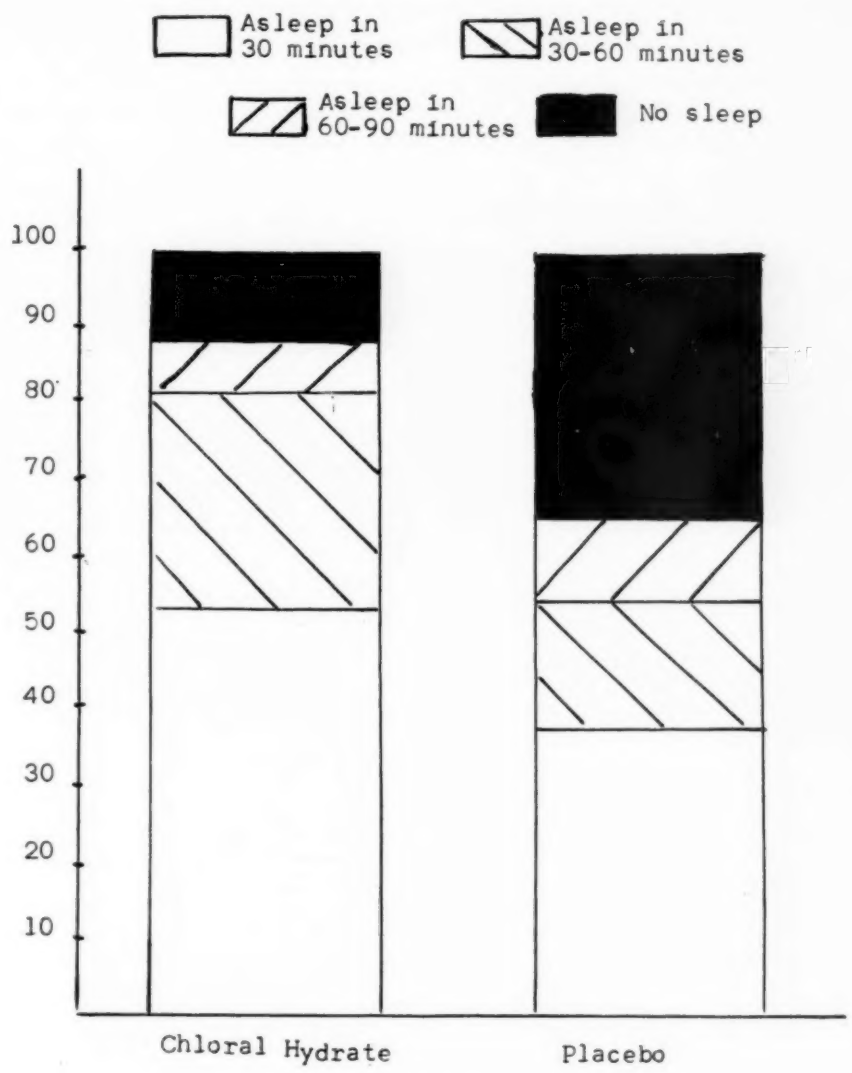


FIG. 1. Time interval before onset of sleep.

even more significant when it is emphasized that this study was not made on the basis of two groups of *patients*, but rather two groups of *records*. Each subject received each of the two preparations, and was in a sense his own control.

Length of sleep

The mean length of sleep for the chloral hydrate group was seven hours, thirteen minutes; for the placebo group it was five hours, fifty-seven minutes.

Undesirable reactions

Soporifics do not always act as the physician wishes. Barbiturates, in particular, frequently stimulate rather than sedate the geriatric patient. We were,

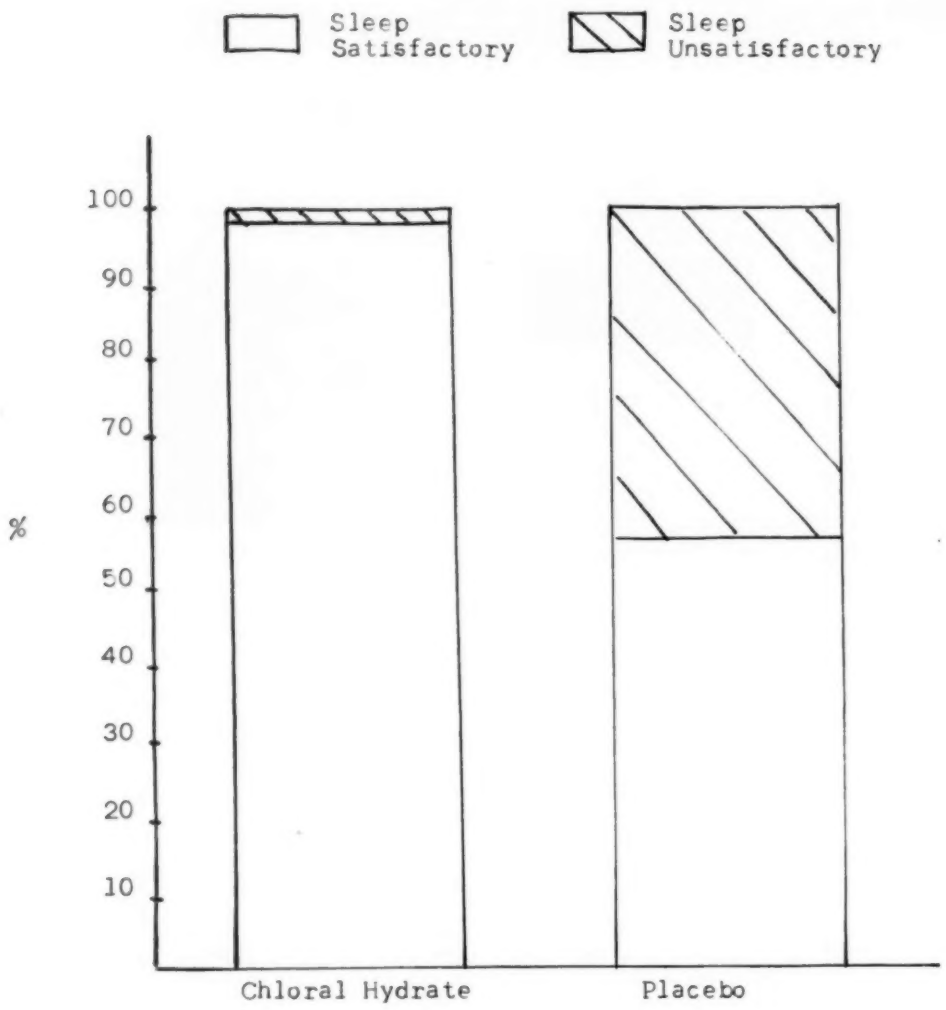


FIG. 2. Patient's opinion of sleep (satisfactory; unsatisfactory).

therefore, interested in determining the number of undesirable reactions. The data are summarized in Figure 3. Surprisingly, 12 patients (16.0 per cent) who received placebo tablets were restless, noisy or excited, but only 4 patients (5.3 per cent) who received chloral hydrate tablets showed similar behavior. To learn whether or not the placebo contained some stimulating principle, the tablets were analyzed; they were found to be composed only of a lactose-sucrose combination. However, many of the total group of patients had chronic disease characterized by pain (*e.g.*, osteoarthritis), dyspnea, or other discomfort. Since no active drug was given in the placebo, the discomfort continued and would naturally be expected to cause a restless night.

Figure 3 also shows the incidence of "hangover"-like symptoms on the following morning. The excretion of chloral hydrate from the body (through the kidneys) is accomplished in from ninety minutes to eighteen hours (2). There-

fore, it would not be surprising to note many cases of morning drowsiness. However, only 3 such cases (4.0 per cent) were found, compared to 9 (12.0 per cent) in the placebo group. We have no explanation for these findings, except on a psychogenic basis.

When chloral hydrate is given in other forms, gastric irritation is the chief problem. With the tablet form used in this study, only 3 instances (4.0 per cent) of gastric irritation were noted, and none with the placebo tablets. No other

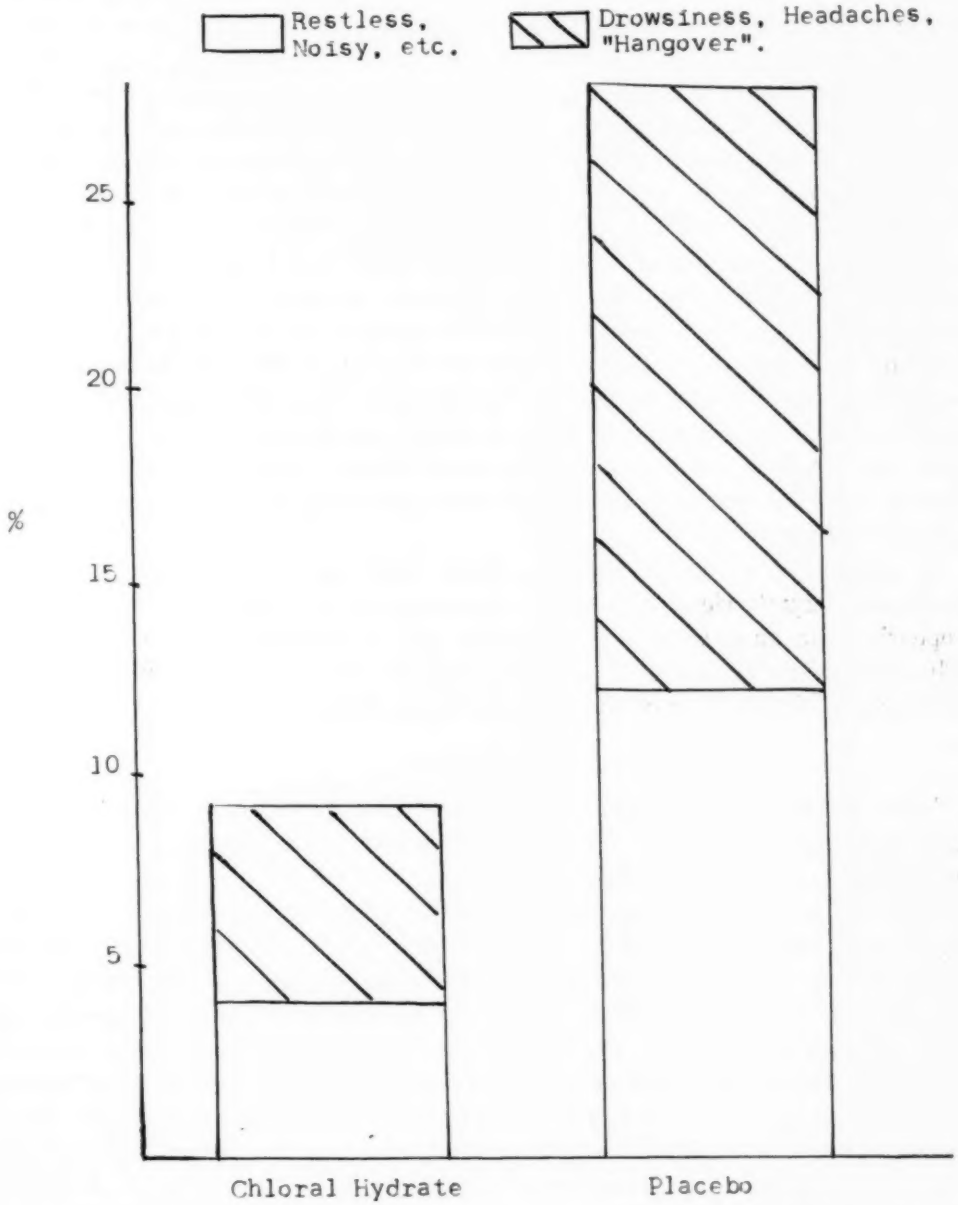


FIG. 3. Type of sleep (restlessness, noisy), and condition the following day (drowsiness, headache, "hangover").

side-effects occurred that were attributable to the drugs, and there was no addiction or habit formation.

COMMENT

After nearly one hundred years of use it seems hardly necessary to elaborate on the safety and effectiveness of chloral hydrate. Rudd (3) has indicated that it should not be used in patients who have severe cardiac disease, but Sollman (2) has pointed out that the fear of excessive respiratory or cardiac depression is based on faulty deductions from animal experiments. Forty-seven per cent of the patients we studied had been taking digitalis or digitoxin for at least six months, and none showed any untoward depressive response. Since chloral hydrate is detoxified by the liver and excreted by the kidneys, it is probably advisable to refrain from giving it to patients who suffer from advanced renal or hepatic disease. As the span of life increases, organic and psychic problems will also increase, and insomnia will continue to be a frequent complaint. When the patient has obvious organic disease that prevents him from sleeping, the treatment is clear. Attention to proper systemic treatment, adequate fluid and nutritional intake, and improvement in the general well-being will permit peace of mind in many patients who would otherwise have difficulty in sleeping. The use of hypnotics should be reserved for those in whom sleep cannot be induced by more general measures (4). When drugs are necessary, chloral hydrate is safe and effective, and this new tablet form presents a nonbarbiturate hypnotic, free of the local irritating effects that have previously limited the usefulness of chloral hydrate.

If administration of an 800-mg. tablet (500 mg. of active drug) does not produce adequate sleep within thirty minutes there should be no hesitation in repeating the dose. Only a few patients will be resistant to the double dose. This tablet form of chloral hydrate is a definite asset in the treatment of elderly persons, and is the drug of choice for inducing sleep.

SUMMARY

The soporific effect of a new tablet form of chloral hydrate in molecular linkage with hexylene glycol was evaluated in 56 geriatric patients in a home for the aged, by use of the double-blind technique.

The initial dose was one 800-mg. tablet (representing 500 mg. of chloral hydrate). This was repeated if the patient was not asleep within thirty minutes. Of those who received chloral hydrate, 87.9 per cent were asleep within ninety minutes, as compared to 65.1 per cent of the placebo group. On questioning, 97.4 per cent and 56.0 per cent respectively thought that the sleep was satisfactory. Stimulation rather than sedation occurred in 5.3 per cent of patients given chloral hydrate, and in 16.0 per cent of those given placebos. Only 4.0 per cent of those who received the active drug had a "hangover" the following morning, but similar symptoms were found in 12.0 per cent of the placebo group, a finding difficult to explain.

The absence of side-effects and local irritation (especially of the gastro-

intestinal tract) indicates that this form of chloral hydrate is a safe and effective agent for managing insomnia in the aged.

Acknowledgments

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MANAGEMENT OF RESTIVE AGED PATIENTS IN OFFICE PRACTICE

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Since 1950, the number of people past 65 years of age in this country has risen from 12 million to 16 million; by 1975, it will be over 20 million. This increase is evident daily in office practice. It is even more evident in the population of our mental hospitals; consider that nearly half of all patients at the time of first admission and one-third of all mental patients in state hospitals are over 60 years of age (1).

With advancing years there is little doubt that symptoms of anxiety, self-censure, regret and loss of self-esteem, which have heretofore remained dormant, emerge and mount in intensity. In men, the reaction may be touched off by retirement; in women, by death of the husband. The management of these patients, especially those whose problems have no organic basis, requires more than the overworked explanation "you're getting on in years," dispensed with a few words of reassurance.

If dismissed lightly by the family physician, elderly people frequently have nowhere to turn, even though they may be part of a family group. Everyday stresses and strains become more than they can cope with, and increase beyond their control; the result is confusion and restiveness. These changes in behavior create domestic problems which, according to Vail (2), tend to be solved by putting those who are unwanted into a hospital for the mentally ill. As he points out, however, the cost is staggering, not only in dollars but in the crippling of other services and in human dignity.

This report is a brief review of some fairly simple measures used over the years and found effective in managing confused and restive aged patients. It is presented in the hope that it will encourage family physicians to take a more active interest in treating such patients in their offices, admitting them to a psychiatric hospital or home only as a last resort.

FACTORS IN MANAGEMENT

Know the patient

The importance of friendly interest while taking the aged patient's history cannot be overemphasized. Evidence that he is a respected person rather than a "case" will do much to shore up the sagging ego of one who has been losing self-esteem as a result of his decreased abilities and lack of productive contributions. The physician should take time, after the examination, to explain to the patient the nature of his ills, the purpose of any laboratory studies, and the proposed treatment. In certain cases, it is well to mention fees, so that exaggerated fears about expenses will not hinder effective treatment. Usually, during the second or subsequent visits, the relief of somatic complaints will establish the

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rapport that was previously lacking or difficult to reach. On the basis of this progress, chances become good for employing effectively such supportive measures as encouragement, sympathy and reassurance.

Determine intrafamily stress

When the patient lives with a married son or daughter, there is a strong likelihood that his emotional unrest is producing a strain on the rest of the household. Quarrels because young grandchildren shatter much-loved routines frequently precipitate matters, and the elderly patient becomes more crotchety and increasingly left out of things. Verbal protest or sullen, disapproving withdrawal creates resentment on the part of other younger family members. Whatever the cause of friction, the physician often can relieve a potentially explosive situation by taking the time to talk with one or more members of the family of an elderly patient whose infirmities make him unhappy, or whose unhappiness makes him ill.

If the rest of the family can accept the fact that the older person's behavior is not unusual or serious, increased tolerance on their part often leads to better acceptance of, and better behavior by, the elderly person. More tact by the family can take the form of listening to the "voice of experience." More positively, they can ask for advice or occasionally remark about some recent or past achievement to bolster the older person's ego. Since the need to be needed does not subside with diminishing capabilities, asking the aged person for advice makes him feel wanted and worthy. Often domestic frictions can be resolved simply by asking for solutions from the parties involved. Fortunately, when members of the aged patient's family are appraised of the patient's condition, they generally become sympathetic, show greater understanding, and often come up with practical solutions.

Manipulate a deteriorating environment

Talking to the patient's family provides a means of sizing up their home life and the sources of stress which, over the years, may reach a breaking point unless there is some change in environment. These are not the family squabbles that pass after a few days, but critical issues that quickly tax the elderly patient's no-longer-flexible nervous system. Fixing blame seldom does anyone any good; in many cases both parties are equally to blame, so it is well to avoid taking sides.

In one case, an intolerable situation was resolved by setting up an apartment for a 58-year-old mother-in-law who felt lonely and rejected and, as a result, experienced epigastric distress, difficulty in breathing and vague aches and pains. Once settled in her apartment she found independence and companionship that was lacking in her son's home, where her tastes in decorating, child-rearing, and just about everything else ran contrary to those of her daughter-in-law. Her aches and pains subsided spontaneously. Moreover, relations between her and her daughter-in-law improved and both heartily agreed that they got along better visiting than living together, and that it was "better for the kids" not to

be exposed to family arguments. Fortunately, in this case, the matter of expenses presented no problem; the mother-in-law had a comfortable nest-egg and her son periodically added to it.

Often social workers or visiting nurses can provide much helpful information on home life. They can readily learn whether the patient is a victim of an uncaring or uncooperative family and, when necessary, provide the names of apartment houses or hotels catering to elderly people with limited financial abilities. The fate of a pensioner in these times is not a happy one.

Environmental manipulation may be necessary even when the elderly person is reasonably well adjusted and the tension is caused by a neurotic younger member of the family. In such a situation, hospitalization of the neurotic is not the answer, but neither is having the elderly patient risk remaining in the hostile home. Generally, a satisfactory solution can be worked out by having the elderly person live apart, but nearby.

Encourage activities and interests

Time weighs heavily on the aged, especially those who have once been fairly active. Minor ills get more of their attention, often becoming a preoccupation. The patient who has given up hobbies he once dabbled in should be encouraged to resume them. If he has no hobby, suggesting one may be well-intentioned advice that will fall on deaf ears unless some member of the family can be enlisted to take an active interest to get the patient started and encourage him sincerely. The aid of perfectionists should be avoided; their carping pushiness will do more harm than good.

It is extremely important for those in their 50's and 60's to keep in touch with friends, if only to go to the movies or shopping, to play cards, or to maintain other interests as much as possible. Even watching television regularly can maintain some interests. For example, a patient who was an athlete in his youth, now in his 60's, contentedly spends his mornings reading the sports pages, his summer afternoons watching televised baseball, and his evenings viewing westerns and boxing. Before television renewed his interest in sports, however, he chafed at unaccustomed inactivity and irritated everyone in his daughter's household by meddling in their affairs and complaining that he was neglected. Although his current viewing taste may be questioned, his excellent adjustment to retirement cannot.

Community facilities can be helpful. Women particularly find that church programs and hospital volunteer work keep them active in genuinely valuable pursuits. Certain community-sponsored social clubs provide the means for them to meet others with similar backgrounds, interests, and memories, and in doing so, make new friendships to counteract the loneliness and feelings of rejection and domination by younger people.

Limit the use of drugs

Despite the large number of drugs available for geriatric patients, not more than a few provide much practical benefit. The physician should select those that he has found to be effective in actual experience, and are reasonable in price.

Much depends on the patient and his problems. One very common complaint is insomnia: the patient either cannot go to sleep when the rest of the family does, or he tends to wake up and wander the hall at 4 a.m. Either way he is in some danger of an accidental fall and is a disturber of the household peace. In such instances, chloral hydrate at bedtime generally solves the problem, without creating others. Barbiturates are sometimes effective, but they are not always well tolerated by the aged and sometimes lead to difficulties because of increased confusion or restlessness.

There are other emotional problems among the elderly which are more complicated and persistent and which require more than simple sedation. In these instances, several of the tranquilizing agents make useful adjuncts to the physician's counselling and the family's understanding. Looking over cases in my practice which have benefited by adjunctive tranquilizer therapy, they can be classified into three groups (Table 1): 1) the maladjusted, perhaps even neurotic, oldster; 2) the patient with great anxiety associated with organic illness; and 3) the senile patient.

EXPERIENCES WITH PROCHLORPERAZINE

The use of tranquilizing drugs should be based on actual experience. Of the variety of phenothiazines and meprobamate, prochlorperazine is well suited for managing elderly patients in office practice.

My records over the past four years show that 103 elderly patients have been given the drug, and that its use presented no toxicity problems, produced a satisfactory calming action, and did not cause excessive daytime sedation. As Table 1 shows, 70 patients (70 per cent) obtained good results, *i.e.*, emotional unrest was relieved, and they became more accessible to counselling and could continue to live at home. In 19 others who showed some improvement in their emotional state and general cooperativeness, the results were rated as fair; 14 patients showed a poor response. None of the latter 14 responded to either chlorpromazine or meprobamate. In 4 of these cases, some of the reasons for failure lay in the fact that the patients were poorly adjusted to situations which simply could not be changed; as long as they remained in their environment, little improvement could be expected.

TABLE I

Therapeutic Results, Duration of Therapy, and Side-effects in 103 Restive Aged Patients Treated with Prochlorperazine

	No. of Patients	Avg. Age (yrs.)	Avg. Duration of Therapy (wks.)	Results with Prochlorperazine			Side-effects
				Good	Fair	Poor	
Neurotic and/or maladjusted	60	68	11.1	36	16	8	3
Anxiety assoc. with organic disease	26	67	15.0	20	1	5	2
Senility	17	79	13.3	14	2	1	0
Totals	103			70	19	14	5

Of the 5 patients reporting side-effects, 3 said they experienced tremulousness, and 2 others reported weakness. These side-effects disappeared when the drug was discontinued.

The outstanding fact in this study—more important than the percentages of subjects improved or unimproved—is that not one of these patients had to be sent to an institution. It was well worth the effort to spend a little extra time in studying these elderly patients' needs, advising them and their families what to expect, and using adjunctive therapy to relieve the anxiety and irritability that often complicates the situation.

SUMMARY

A review is presented of some simple effective measures in the management of aged restive patients, which may be overlooked under the pressure of a busy practice. Many elderly patients may be cared for at home, thereby reducing the rising number of geriatric admissions to psychiatric hospitals.

For effective management, the physician must first get to know the patient as an individual, and become familiar not only with the patient's physical condition but also with his emotional problems and any stress situations that contribute to his tensions. Being thoroughly familiar with the situation aids immeasurably in proper counselling of the older patient and his family and in manipulating environment for the greatest benefit of all.

Only by knowing the patient and the community in which he lives, can the physician hope to make sensible suggestions about activities and organizations that offer new interests and companionship to elderly patients distressed by feelings of increasing helplessness.

The use of drugs should be limited to those of proven merit. Chloral hydrate is best suited for sleep disturbances, and prochlorperazine for the more persistent emotional problems in the aged.

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BACKACHE IN THE AGED: THE VALUE OF CORRECTIVE EXERCISE

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The ubiquitous problem of the aching back is apt to be as common among the senior citizens of any community as it is among adults of all ages who seek relief. The etiology, however, differs somewhat from that in younger age groups. Compression fractures of the vertebrae are far more common in the elderly (2). Traumatic compressions are third in frequency among all fractures in this age group (3). Benign spontaneous compressions add considerably to the number; these are common in senile osteoporosis, though not all are persistently symptomatic (4). Compression of the intervertebral discs causes symptoms far less often in the aged than in the middle-aged, since generalized degeneration of the discs is a normal accompaniment of the aging process. For the most part, this degenerative process is compensated for by decreased elasticity of the paravertebral ligaments, lessened resiliency of the intervertebral joint surfaces, and the stabilizing effect of vertebral osteophytosis (5). Degenerative osteoarthrosis of the aging spine, on the contrary, is one of the more common causes of disabling back pain.

Vertebral osteoporosis can provoke severe pain in the back and persistent disability in the aged. The pain is clinically differentiated from that of osteoarthrosis by its tendency to persist with equal severity at rest. It may or may not be accompanied by spontaneous compression fractures, and may become worse during any prolonged period of rest without weight bearing, either enforced or elected (1).

Rheumatoid arthritis of the spine and the Marie-Strümpell syndrome are seldom found in the aged, unless in the final stages when the vertebrae are fused and usually cause no symptoms. In the aged, with their relatively rigid spines, strains of specific vertebral ligaments are less frequent, but postural strain due to persistent imbalance is common. Inflammatory rheumatic myofascitis—the legendary "lumbago" of unknown specific etiology—is common in the "younger elderly" and quite uncommon in persons in the late 70's or older. Spondylolisthesis is usually an incidental finding associated with backache; in the aged person it is either well compensated for, or has already reached a stage requiring aggressive surgical intervention; thus it is unlikely to be a cause of the backache. Neoplastic metastases to the vertebra, unfortunately, are common in the aged; they will not be discussed here since they represent a therapeutic problem of a different order.

The different forms of backache call for a variety of therapeutic measures, *e.g.*, drugs, hormones, physical modalities, and at times immobilization by corsets or braces. During periods of severe pain the patients all seek rest, either

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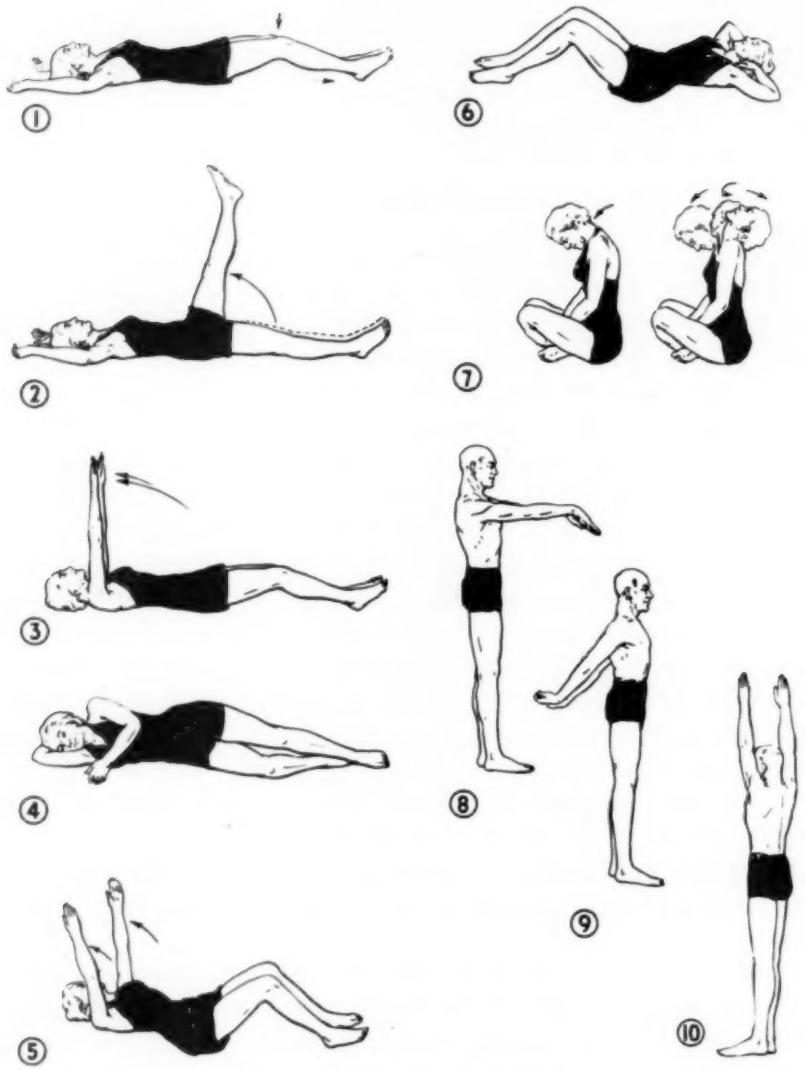

FIG. 1. *Pelvic tilt.* In supine position simultaneously inhale while drawing the abdominal muscles upward and inward and contracting gluteal muscles; hold contraction; slowly exhale while releasing contraction.

FIG. 2. *Alternate leg raising.* In supine position, keep right leg in complete extension; slowly raise left leg upward, keeping knee in extension; hold; slowly lower left leg, being careful to maintain smooth control until heel touches floor/table; repeat with right leg. (In older group, 70% extension is sufficient.)

FIG. 3. *Upward arm extension.* In supine position with arms at sides, slowly raise arms, stretching upward and backward above head, inhaling deeply; hold; exhale while slowly returning arms to starting position.

FIG. 4. *Knee slide.* Lying on right side with right arm stretched upward and left arm over table for balance, slowly draw up right knee to abdomen; hold; slowly return knee to starting position; repeat on left side.

FIG. 5. *Vertical arm extension.* In supine position with arms at sides, slowly bring arms up vertically while inhaling deeply and pulling up knees; hold; slowly lower arms to sides while exhaling and sliding heels until legs are in complete extension.

on advice or of necessity. Partly because of relative inactivity, partly from positional strain, and often because of frequent periods of enforced rest, there is a tendency toward weakness in the erector spinae and related muscle groups. Such weakness in the postural mechanism either makes the backache worse or prolongs it. Correction of this weakness, as in the younger adult, not only tends to restore normal balance, but adds considerably to the general strength and agility of the body (6, 7).

EXERCISES

The authors have been particularly interested in the problem of backache in the aged for some years and have experimented with various forms of exercises suitable for this age group (3). One of us (E. G.) has taught and supervised corrective exercises for back pain in adults for the past seven years. It was noted that many of the exercises customarily used in such cases involve flexion and lateral bending of the spinal column. The semirigid, arthritic or osteoporotic vertebrae of the aged seldom tolerated these standard procedures. Irritation of the intervertebral joints, and strains of the paravertebral ligaments tended to aggravate the original symptoms or provoke new ones. The older patients were often quite pleased with the idea of exercise, at least in the early stages of their disability, and regretted that they could not continue. It was then realized that a set of exercises was required which would stimulate and strengthen the erector spinae and the associated spinal muscles, and that this should be accomplished chiefly by movements of the limbs, with a minimum of vertebral motion.

The set of exercises described here (Figs. 1–10) was designed as being the most suitable for the purpose. These exercises have been developed and used over a five-year period and are considered sufficiently effective to merit presentation for the use of others concerned with the rehabilitation of the aged. Obviously not all are required for each case; they should be selected to suit the individual capabilities of the specific patient. An intelligent and sympathetic approach is most helpful. To some extent the patient is permitted to choose the exercises best adapted to his own agility. In all elective therapeutics in the aged this is a

FIG. 6. *Abduction-adduction movement of shoulder blades.* In supine position with hands at back of neck and elbows at right angles, bring elbows forward; slowly push elbows backward drawing shoulder blades to midline; hold; relax.

FIG. 7. *Head rotation.* Sitting with good postural trunk alignment and hands in lap completely relaxed, let head drop forward; turn to left; continue to rotate backward and around to right in as large a range as possible; continue rotation forward to starting position.

FIG. 8. *Forward arm raising* (sitting or standing); stand in good postural position contracting abdominal and gluteal muscles; arms at sides; hold contractions and bend hands backward at wrists; slowly raise arms forward to shoulder height; hold; slowly lower arms while relaxing contractions.

FIG. 9. *Backward arm rotation.* Stand in good postural position; raise arms backward and upward; make fist, and bend wrists backward; rotate both arms backward, drawing shoulder blades together; hold; slowly release and return to starting position.

FIG. 10. *Upward stretch.* Stand tall in good balance; contract abdominal and gluteal muscles; slowly bring arms up straight overhead, palms facing; from waist, draw trunk upward, extending fingers toward ceiling; hold; slowly lower arms while releasing contractions.

valuable principle, and in the field of corrective exercises it is particularly profitable.

COMMENT

Not all patients with back pain who perform these corrective exercises are remarkably improved. However, when properly conducted in suitable cases the exercises are as efficacious in relieving symptoms and restoring comfort to the ailing back of the aged person as they are in the younger adults. As an adjunct to a broad regimen of care, they can be amazingly effective.

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TUBERCULOSIS OF THE LONG BONES:

Case Report

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The long bones are a rare site of tuberculous infection, particularly in the adult. Nevertheless, in authenticated cases, the special aspects of diagnosis and the treatment are so important that it seemed of interest to report the following case:

A 59-year-old woman with hypertension had pain in the middle third of the left leg which had commenced three to four months previously and had grown worse during the week before admission to the Hôtel-Dieu St. Vallier. The pain was aggravated by movement and compression, but was alleviated when the patient was at rest or in the supine position.

The history was unremarkable. The patient had consulted a physician only at the time of a pregnancy that was normal in all respects. There was no history of tuberculosis in the patient or her family. She had the appearance of a normal woman aged 59 years. Her blood pressure was 180/100 mm. Hg. The middle third of the lower left limb showed slight pitting edema. Sharp pain was induced by palpation, and subcutaneous tumefaction was noted. Aside from these observations, there was nothing by which a diagnosis could be established clinically. Initial laboratory examinations showed a leukocytosis of 11,680 and a normal urine. The electrocardiogram demonstrated left axis deviation.

The first impression was of a bony tumor. Therefore, a roentgenogram was obtained. This showed no discrete bony lesion but a thickening of the tibial periosteum, possibly in association with disturbances of the venous circulation. Additional laboratory tests showed normal serum alkaline phosphatase activity, absence of Bence Jones proteins in the blood and urine, and the presence of C-reactive protein. The erythrocyte sedimentation rate at this time was 31 mm. per hour. A Van Slyke test showed a urea clearance of 93 per cent.

The preoperative diagnosis (pathologic examination of bone) was multiple myeloma. At operation the surgeon noted periosteal thickening about the tibial diaphysis but the bone appeared to be normal.

Since no diagnosis could be made on the basis of the operative findings, biopsy specimens were obtained from both periosteum and bone. Surprisingly, histologic examination of the periosteum showed an inflammatory granular reaction with lymphocytes, histiocytes, Langhans' giant cells, and bony necrosis. A few follicular arrangements could be seen, although the section of the decalcified bone was poorly prepared. The pathologic diagnosis was tuberculosis of bone. Roentgenograms of the vertebral column and lungs showed no tuberculous lesions. The laboratory confirmed the diagnosis of solitary, primary tuberculosis of the diaphysis of a long bone.

Treatment consisted of the administration of streptomycin and iproniazid (Marsilid) with appropriate therapy for hypertension. Under this regimen, the tuberculosis was rapidly controlled. Pain disappeared within ten days and the erythrocyte sedimentation rate fell to 18 mm. per hour by the twenty-fifth day. The patient returned to her home. She continued treatment under observation and made periodic office visits. She improved

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constantly and recovered completely. Three months after beginning treatment, roentgenographic examination showed that the periosteum was no longer thickened and the bone was completely normal.

DISCUSSION

This case is noteworthy because of its rarity and because it presented a problem in diagnosis and treatment, particularly in view of the patient's age. Diaphysial tuberculosis is said to represent less than 1 per cent of all cases of osteoarticular tuberculosis, and to be found more often in children, especially in the lower limbs.

The etiology and pathogenesis were problems from the start. We favor the microbial embolus theory, inasmuch as the patient seemed to enjoy good health, lived in a healthy environment, and could recall no trauma to the affected leg.

The clinical findings agreed with those previously reported for similar cases, namely, pain (in situ), slight tumefaction, no noticeable loss in weight, and no alteration in the general condition; the pathologic findings were also the same. The patient's age and the bone picture in the first roentgenogram led us (like other authors) to the mistaken diagnosis of a bony tumor. A bone biopsy (including periosteum) was necessary before the proper diagnosis could be made.

Once the lesion was diagnosed as tuberculous, treatment posed a serious problem. Opinions in the literature regarding therapy are contradictory. The partisans of surgical intervention oppose arguments for a medical regimen. We chose chemotherapy, because of the patient's age, the presence of hypertension, the prolonged immobilization, and the efficacy of modern chemotherapeutic agents in other cases of diaphyseal tuberculosis. The results were favorable. The symptoms disappeared, and at the time of follow-up examination the clinical findings, the erythrocyte sedimentation rate and roentgenograms indicated complete recovery.

SUMMARY

A case of diaphyseal tuberculosis of the tibia is presented. The diagnosis was confirmed histologically. The disease was treated successfully with streptomycin and iproniazid.

THE HISTORICAL DEVELOPMENT OF PROPRIETARY NURSING HOMES IN CONNECTICUT

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The initial step toward the creation of adequate nursing homes in Connecticut was made in 1873 by the establishment of the State Board of Charities under statutory provisions. This event marked the beginning in Connecticut of an effort to abolish the practice of farming out aged and indigent persons to the lowest bidder and to insure a more humane treatment of the state wards. However, it was not until 1917, as the result of a scandal, that the Board became concerned about the care of elderly people. In that year, a Mrs. Amy Gilligan of Windsor, who operated a boarding home for elderly men, was arrested on suspicion of murder following the questionable deaths of several of the boarders. Upon investigation it was found that she had been slowly administering poison to some of the inmates and subsequently collecting the insurance. Mrs. Gilligan was convicted of murder and sentenced to life imprisonment. As a result of this scandal a law was passed which required a home, caring for two or more persons over the age of 60, to be licensed by the State Board of Charities. Ten years later, in 1927, the licensure law for chronic and convalescent hospitals was passed. The first chronic and convalescent hospitals were licensed in 1928 by the doctors in the Bureau of Preventable Diseases of the Connecticut State Department of Health. It is noteworthy that nursing homes have always been known as chronic and convalescent hospitals and have been licensed as such in Connecticut. Practically all the nursing homes were run by women in their own homes. They had no hospital or nursing experience. In 1935 these women were made practical nurses, through an open waiver.

One of the earliest nursing homes in Connecticut (Fig. 1) was started on February 11, 1920, by Mrs. Susan Griggs in the Town of Norwich. She was asked by the city missionary to take an 89-year-old woman into her home and care for her. The patient, Miss Julia Miles Standish, was being discharged from the Backus Hospital and had no place to go. This patient was a direct descendant of Captain Miles Standish. Before she died at the age of 95, she stated that the home had been a "haven" to her. It has been called "The Haven" ever since.

The success of this placement prompted the Backus Hospital to send Mrs. Griggs 2 more patients. The Town of Norwich paid her $15.00 per week for each patient. About a year later Mrs. Griggs moved to Pomfret, Connecticut, and took her patients with her. She took care of them, did the cooking and cleaning

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FIG. 1. Elm Cottage, February 11, 1920. Mrs. Susan Griggs opened this little cottage at 97 Summit Street, Norwich, as a home for the aged—one of the earliest nursing homes in Connecticut.

and hand-washed the laundry. Rather than hire help, her husband decided to stay home. Anyway, he was becoming very tired of riding his bicycle several miles each day to and from work. The next Christmas the neighbors became interested in doing something for the patients and as a result a human interest story was written up in the local newspaper. A few days later Mrs. Griggs received a letter from the Board of Charities informing her that she would have to have a license to board these elderly people. She was among the first to be licensed to operate a nursing home.

That same year, in 1928, Mrs. Griggs' daughter became very ill. The family hired a registered nurse to take care of her. When Mrs. Griggs saw how capably the nurse cared for her daughter, she was asked to stay on and help with the other patients. Mrs. Griggs is now in her late 80's, but is still around to see that her son operates the hospital in accordance with her own high standards.

EFFECT OF DEPRESSION YEARS ON THE CARE OF THE INDIGENT, AGED AND INFIRM

This type of hospital did not change much until the early 1930's when the effect of the depression years suddenly awoke an indifferent public to the urgent needs of an increasing number of chronically ill and indigent geriatric patients. This led to the passage of the Federal Social Security Act in 1935. In April of the following year the first Public Assistance Grant of $7.00 per week was made. This was increased to $9.00 per week in 1939 and to $40.00 per month in the

following year. These rates were not too attractive to the operators of nursing homes. However, a few private patients were beginning to be admitted and several small hospitals opened which catered only to people of means. Federal regulations forbade assistance to persons in state institutions and alms houses, as well as to nonprofit church homes and fraternal homes. In order to qualify for old age assistance, people who were eligible had to be placed outside of these institutions. This was the beginning of the expansion of proprietary nursing homes. Another factor was the one which in 1943 allowed old age assistance beneficiaries medical and hospital expenses in excess of $40.00 per month.

CREATION OF THE COMMISSION ON THE CARE OF THE CHRONICALLY ILL

For many years it was felt that there was a need for a State Infirmary to care for the chronic and convalescent patients. In 1943, the General Assembly authorized a study to be made by the Public Welfare Council under the direction of Dr. Karl Heiser. The findings of this body included recommendations "that chronically ill patients need intensive nursing, medical and surgical care and that it can be given only in properly equipped and staffed hospitals" and "that residents in homes for the aged should have a recreational program and an attendant nurse who could call a physician when necessary." To meet these needs, the study recommended that five infirmaries be erected in strategic locations. These were to house approximately 4000 patients. This recommendation caused a

FIG. 2. Seaside Nursing Home, Milford, Connecticut, designed and built for the comfort, convenience and good care of the patient.

FIG. 3. Seaside Nursing Home, showing part of kitchen equipment.

great deal of apprehension among the owners of the nursing homes in Connecticut. It would remove all State patients from their institutions. Fortunately for everyone concerned, these 1000-bed infirmaries did not materialize. However, the 1945 General Assembly created a commission on the care of the chronically ill under the direction of Dr. A. Nowell Creadick, and facilities for rehabilitation were provided at the Rocky Hill Veterans Hospital. Patients were admitted and the results were so gratifying that doctors as well as the state agencies realized what could be accomplished.

To relieve overcrowding in the mental hospitals, Governor Lodge in 1948 authorized payments of $50.00 per week to nursing homes for the care of elderly mental patients. The higher rate was given to increase the staff and provide recreational and occupational programs. It was never felt that the homes fulfilled the requirements for this program, and a great deal of ill feeling resulted on account of the higher rate.

EXPANSION DUE TO ELIMINATION OF CEILING ON GRANTS

In 1949 the ceiling on grants was eliminated and a rate of $5.00 per day plus extras was paid by the Welfare Department. This caused a marked increase in the number of nursing homes. In 1951, the State Welfare Department authorized payment of medical expenses to patients in municipal institutions. This encour-

aged new facilities in large institutions like the McCook Hospital in Hartford, the Hillside Home and Hospital in Bridgeport, and the Municipal Hospital in New Haven, Connecticut.

EVENTS LEADING UP TO THE ENACTMENT OF THE FIRE SAFETY CODE

In 1945, on Christmas Eve, 20 aged and ill patients were burned to death when a three-alarm blaze swept the Niles Street Convalescent Hospital in Hartford, Connecticut. The fire was caused by faulty wiring on a Christmas tree. The fire went out of control during a delay caused by the inaccessible position of a telephone which was so close to the blazing tree that it could not be reached. As a result of this holocaust a statewide investigation of fire prevention equipment in private hospitals and nursing homes was launched, which resulted in the revocation of the licenses of several establishments and in the adoption in 1957 of the Fire Safety Code. This code provided that nursing homes must be of noncombustible construction throughout. It also enacted a law requiring the installation of automatic sprinklers. It further provided that each nursing home housing 15 or fewer patients must have at least one attendant on duty at all times. Other specific regulations designed to protect the aged and infirm from fire hazards were also written into the code by the State Fire Marshal. After

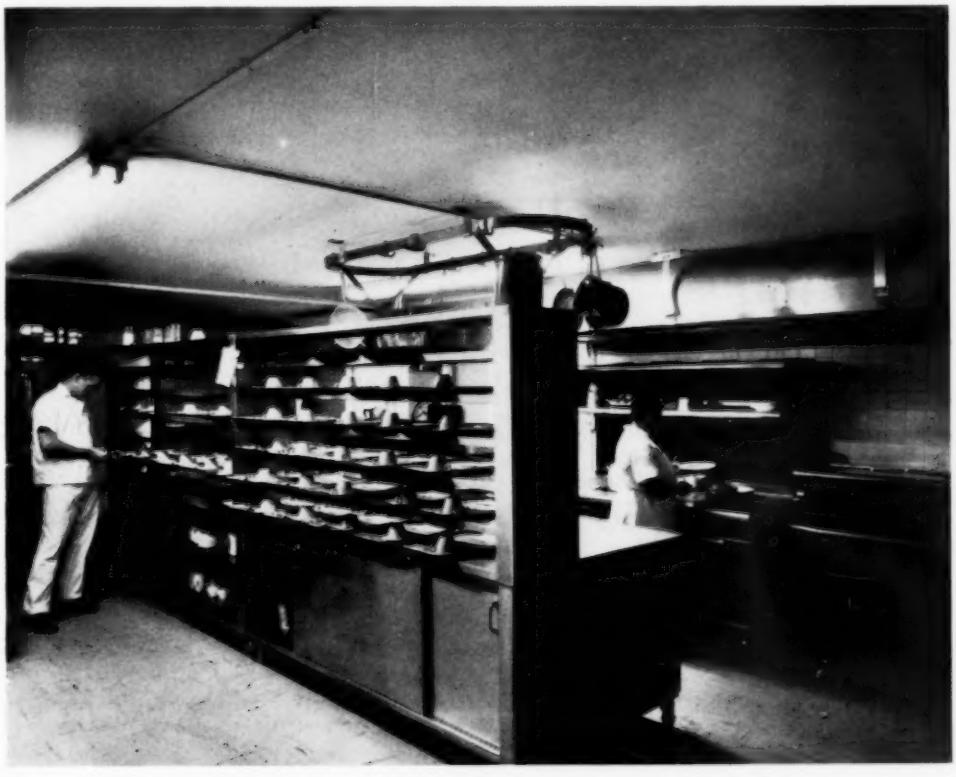

FIG. 4. Seaside Nursing Home. The kitchen is large, airy, fully tiled, and completely fitted with stainless-steel equipment. Food is prepared with strict adherence to the doctor's orders.

FIG. 5. Seaside Nursing Home. The dining room. Use of the dining room is encouraged, though room tray-service is provided.

the adoption of this code the nursing-home operators made strenuous objections and complaints about the expense, but they were nevertheless forced to meet the code.

ESTABLISHMENT OF THE DIVISION OF HOSPITALS

In May 1950, the Division of Hospitals was inaugurated as a separate division responsible for the licensing of nursing homes under the direction of a full-time medical chief. On July 1, 1953, the Division assumed responsibility for the licensing of all general hospitals, and homes for the aged, as well as for chronic and convalescent hospitals. New policies were established and new regulations introduced. Operators were not too resistive to these new policies and most of them willingly complied. Under this new policy, which is governed by statute, both the operator and the licensing agency are fully protected.

In 1957 the Sanitary Code was adopted to increase the efficiency of the Division of Hospitals. This code has worked exceptionally well and the operators have cooperated in every way.

The increase to $7.50 per day for Welfare patients brought a wave of new modern construction of nursing homes which were financed mostly through large corporations.

ADOPTION OF THE NEW SANITARY CODE

On August 25, 1960, the new sanitary code regulating nursing homes was adopted. Specific provisions were made relating to the construction and maintenance of the buildings as well as for the housing, care and safety of the patients.

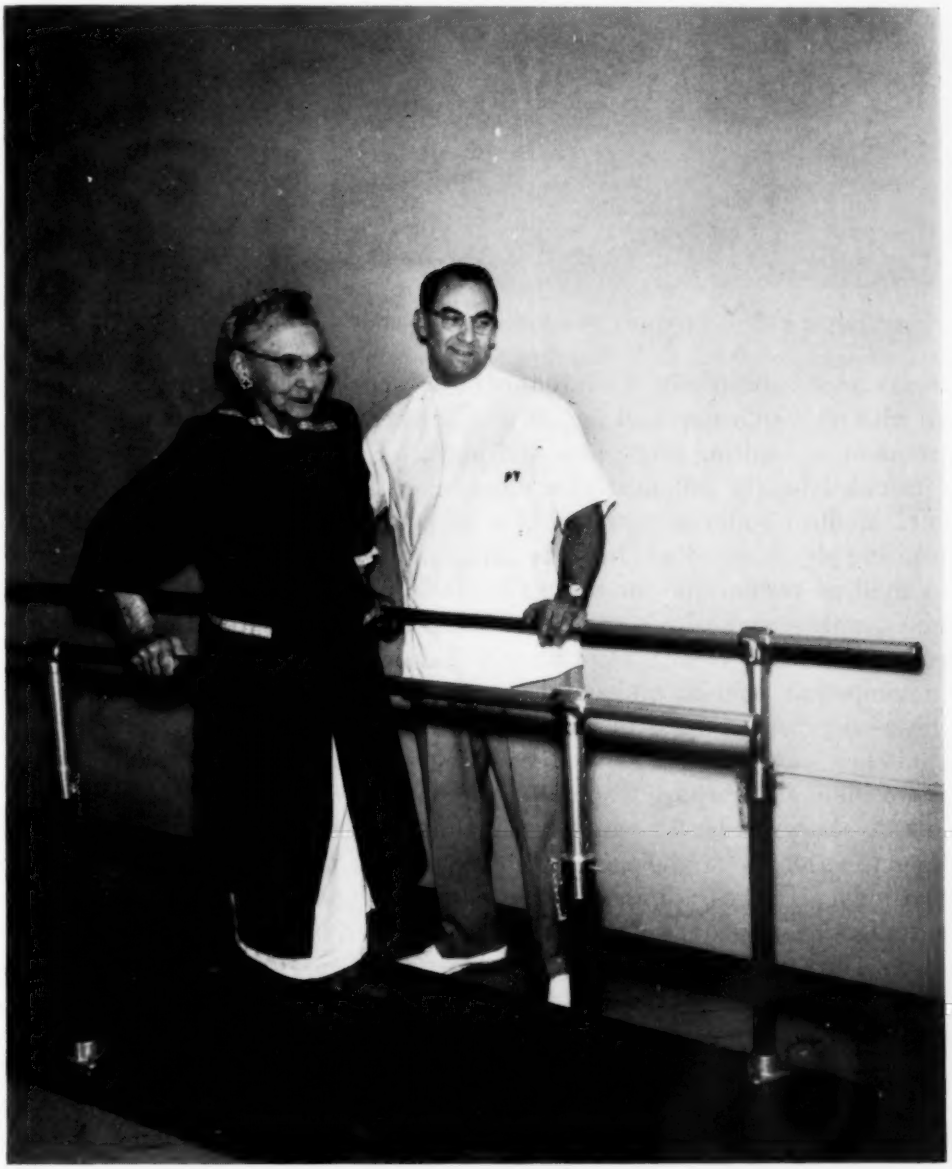

FIG. 6. Seaside Nursing Home rehabilitation program. A 92-year-old patient with a fractured left hip was admitted on October 5, 1959, bedridden, and with a large open bed sore on the left buttock. On November 3, 1960 (this photograph), after a course of physiotherapy treatments three times a week and other rehabilitative measures, she could walk 200 feet with a hand-walker and needed less help with the activities of daily living; the deep bed sore had healed.

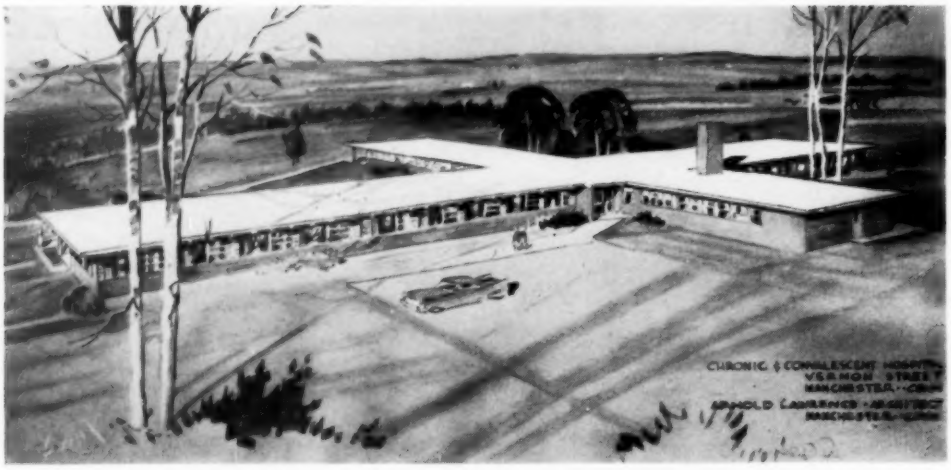

FIG. 7. Example of a modern Connecticut nursing home.

Various responsibilities of the administrator were outlined in regard to compliance with all regulations and for the appointment of a qualified house physician or resident, consulting physicians and nurses. Under the code, references must be provided by the administrator concerning his ability to operate a nursing home. Medical supervision must also be provided by a qualified resident or consulting physician who is to be available at all times in case of emergency and who shall be responsible for the general adequacy of the medical and nursing care. Complete medical records must be kept in accordance with provisions laid down by the State Health Department. The nursing service must be in charge of a competent licensed nurse and there must be at least one registered nurse or licensed practical nurse in uniform on the premises at all times. All dietary and kitchen services, such as food handling, preparation of menus, sanitation, dish washing, and garbage disposal must comply with health board regulations. The code also provides for various general and specific conditions relative to the proper functioning of the nursing home, such as visiting hours, special diets, recreational activities, admission of patients, reports of accidents or other unusual occurrences, maintenance of proper heat, hot water, ventilation, adequate housekeeping, laundry services and innumerable other items.

THE ESTABLISHMENT OF THE CONNECTICUT CHRONIC AND CONVALESCENT HOSPITAL ASSOCIATION

The nursing homes, which in Connecticut are known as chronic and convalescent hospitals, have formed a voluntary association known as the Connecticut Chronic and Convalescent Hospital Association. It is a member of the Joint Council to Improve the Care of the Aged. The Joint Council is composed of the American Dental, American Hospital, American Medical, and the American Nursing Home Association. The objectives of the Joint Council are to identify and analyze the health needs of the aged; to appraise available health resources for the aging, and to develop programs to foster the best possible health care for the aged regardless of their economic status.

Nursing homes may join the Connecticut Chronic and Convalescent Hospital Association by meeting certain qualifications laid down by their Standards Committee. These include the regulations set down by the Sanitary Code of the State of Connecticut governing the operation and maintenance of nursing homes. There are about 216 or more nursing homes in Connecticut about half of which belong to this association. Examples are shown in Figures 2–7.

SUMMARY

From a very modest and humble beginning, the nursing homes in Connecticut have come a long way during the past thirty-two years. In the past decade they have become a modern and efficient adjunct to the general hospital in the continuing care of the aged and infirm. At the same time, however, they have maintained a definite and separate identity of their own.

Nursing homes have formed a distinct social pattern, and a further increase in the efficiency of long-term care of the geriatric patient with his multiplicity of chronic diseases may be anticipated as the joint effort between state and welfare agencies increases in scope.

CRYOTHALAMECTOMY—HYPOTHERMIC CONGELATION: A TECHNICAL ADVANCE IN BASAL GANGLIA SURGERY

Preliminary Report*

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Department of Neurosurgery, St. Barnabas Hospital, New York, N. Y.

During the past eight years, in a continuing series of articles in this Journal (1–3), we have reported a number of successive investigations aimed at establishing basic principles and improved techniques for basal ganglia surgery in humans. It is the purpose of this report to call attention to a new technical

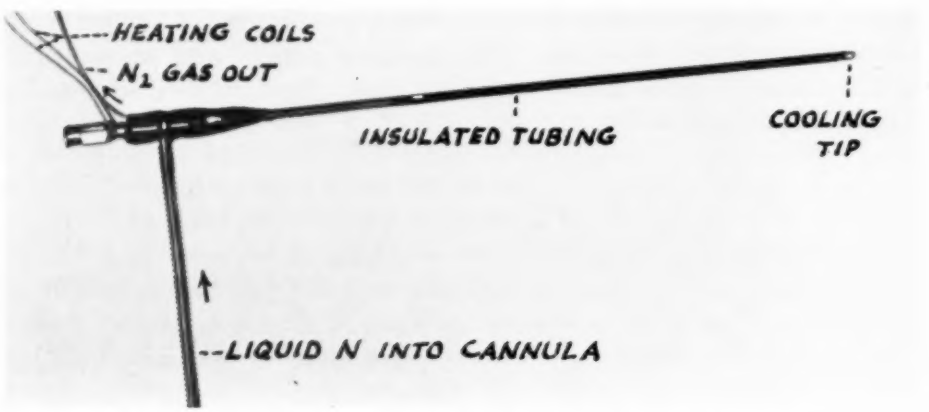

Fig. 1. Insulated brain cannula developed for cryothalamectomy

development which we believe marks an advance in deep intracerebral surgery for the relief of hyperkinetic and allied disorders in man.

It has been amply documented that tremor, rigidity, dystonia, chorea, hemiballismus, intention tremor and other involuntary motor manifestations are totally reversible by properly placed lesions deep within the cerebrum (3–10). However, in order to achieve relatively certain clinical results with a minimal risk of morbidity or mortality, it has become obvious that one must use a clinicophysiologic type of procedure; that is, it must be possible to produce a test or reversible lesion deep within the brain and observe its effects in a conscious cooperative patient before proceeding with the infliction of a permanent destructive lesion (11). This thesis has been amply reported in the past. Moreover, our methods for producing physiologic tests, first by procaine injection and later by development of the balloon cannula used in basal ganglia surgery, have been previously reported.

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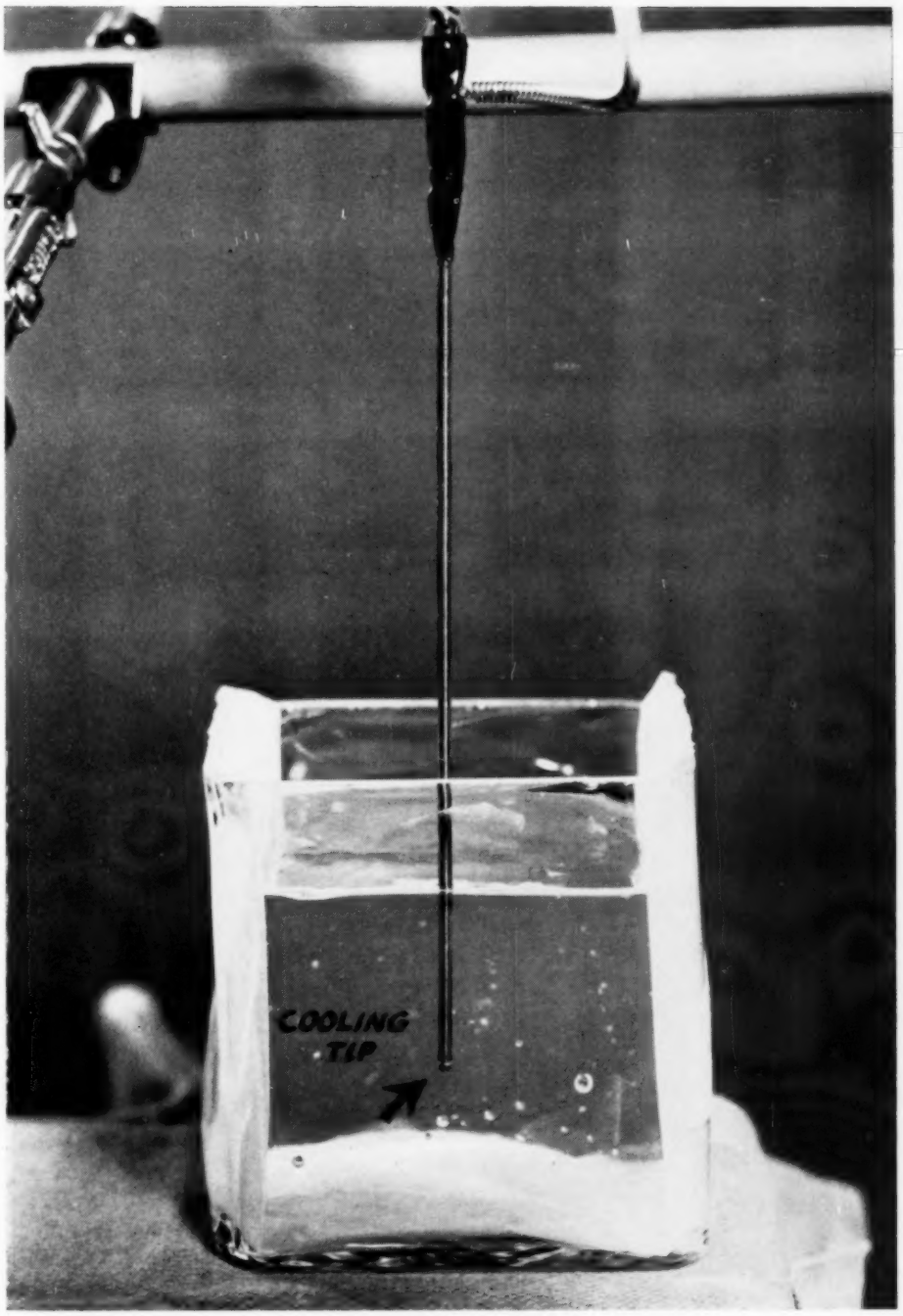

FIG. 2. The cooling brain cannula placed in clear gelatin which approximates specific gravity and consistency of brain. This demonstrates method for *in vitro* production of a lesion.

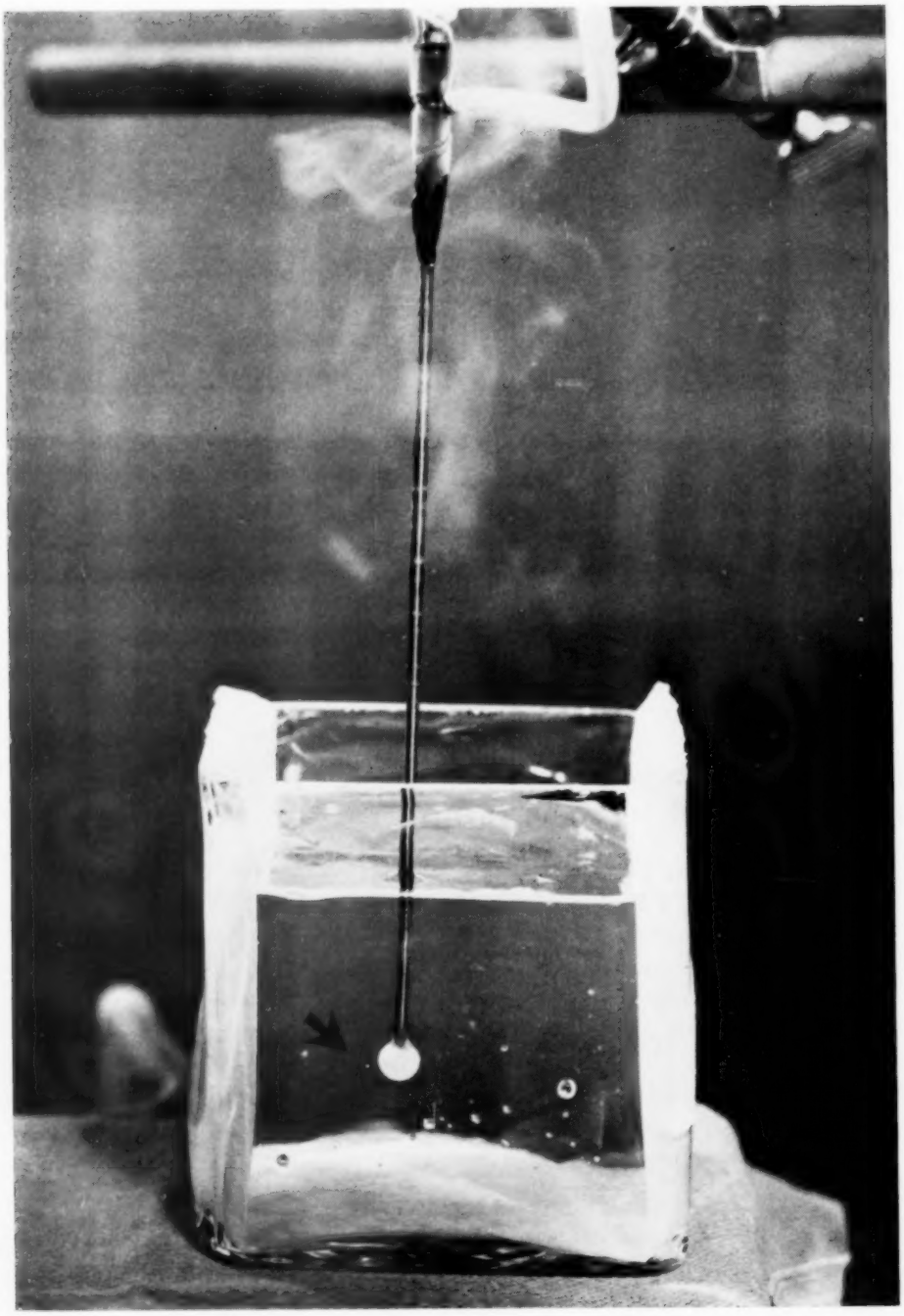

FIG. 3. Frozen maximal lesion produced by cooling cannula in gelatin. Insulation of cannula prevents freezing at any other point than the exposed cooling tip.

In a continuing attempt to improve the safety margin of this type of physiologic surgery as well as the certainty of the clinical results, we have carried out an investigation during the past year aimed at the development of a cooling system which would enable us to produce reversible physiologic nerve blocking followed by infliction of a permanent lesion by the means of controlled freezing deep within the brain. This investigation has led to the development of a special cannula which is capable of producing a limited, controlled region of cooling and/or freezing of biologic tissue *in vitro* or *in vivo*. The ability of cold to produce temporary physiologic blockage of nerve conduction or permanent necrosis both peripherally and centrally is well known (12–15).

The source of cooling used in this system is liquid nitrogen with a temperature of minus 196°C. This is fed by means of a flexible, insulated coil into the brain cannula (Figs. 1 and 2). The cannula is constructed of an inner tube, an outer tube and a tip made of corrosionless, high-strength, hard stainless steel. This is insulated by being wrapped with an electrically conductive copper wire with a large temperature coefficient of resistance.

Liquid nitrogen is fed into the cannula at a pressure of 22 pounds per square inch above atmospheric pressure. It is delivered to the tip of the cannula, at which cooling or freezing takes place up to a maximum of 4 mm. on either side of the center of the tip. The remainder of the cannula is kept at body temperature by the insulating conductor copper coil. Liquid nitrogen is brought to the tip of the cannula through the inner tube. As its temperature rises at the

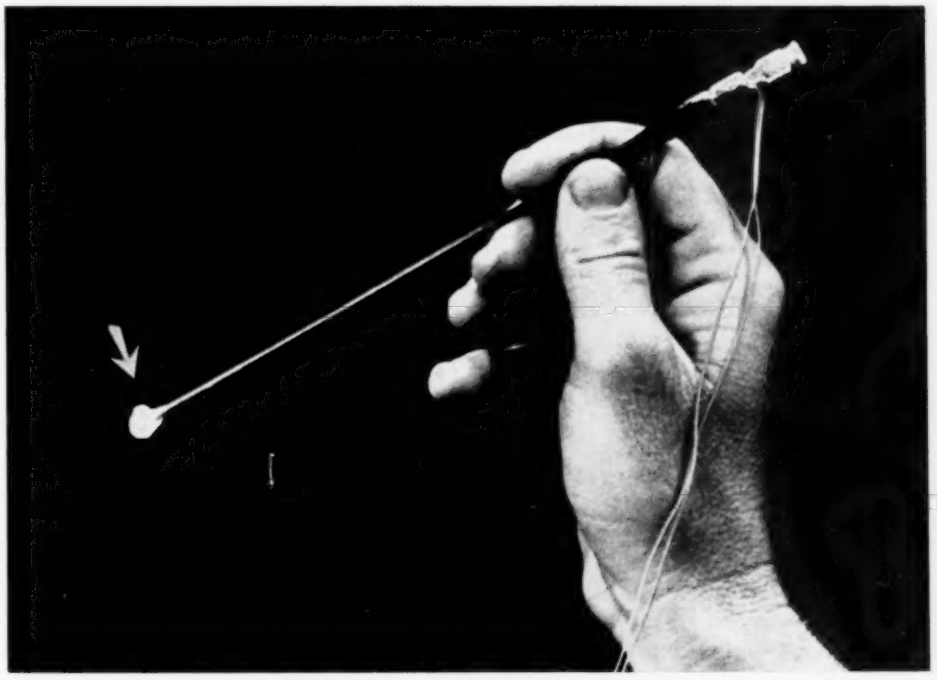

FIG. 4. Demonstration of adherence of frozen plug to the cannula immediately upon conclusion of lesion formation. After a few moments, the frozen plug is no longer adherent.

hollow tip, the gaseous nitrogen escapes through the outer tube and is removed by vacuum suction.

Investigations carried out thus far have demonstrated that this system is capable of producing localized cooling or destructive freezing at the tip of the cannula *in vitro* or *in vivo* (Figs. 3 and 4). This particular model of the cannula is constructed so that the maximal lesion produced will not be greater than 8 mm. in diameter.

Advantages of this method of physiologic nerve blocking and permanent lesion infliction are as follows:

1. Reversible blocking of nerve conduction can be produced in a conscious cooperative patient in order to provide clinicophysiologic testing.
2. A consistent, spherical lesion with a maximal diameter of 8 mm. is produced.
3. The risk of deep intracerebral hemorrhage is mitigated.
4. The system is flexible so that by modification of the cannula or of the refrigerating gas, various sized maximal lesions can be determined.
5. The method is adaptable to physiologic or functional neurosurgery throughout the nervous system.

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Abstracts of Current Literature

EXPERIENCES WITH FIBRINOLYSIN IN PERIPHERAL VASCULAR OCCLUSIVE DISEASE.
Anlyan, W. G.; Deaton, H. L.; Silver, D.; Webster, J. L., and Spada, E. K. *Am. J. Cardiol.* **6:** 507 (Aug.) 1960.

Of 23 patients treated with fibrinolysin, 9 received adequate dosage (300,000 units in twenty-four hours) and were evaluated objectively. The agent was shown to promote the lysis of fresh clots in the vascular system. In 6 patients who had fresh arterial thromboses of three to fifty hours' duration, the results were judged satisfactory. The pulses in the affected vessels returned and the limb or a significant portion of it could be salvaged. In 1 of the 9 patients, fibrinolysin was used prophylactically after arterial trauma and repair. No thrombosis occurred postoperatively. In 1 other patient, thrombosis recurred after fibrinolysin was discontinued. It had restored the pulse postoperatively in a patient who had undergone thromboendarterectomy for arteriosclerosis obliterans. One patient failed to benefit when fibrinolysin was administered following embolectomy for an old organized embolus. An unusual finding was hyperfibrinogenemia in 2 patients. These were 2 who benefited moderately from the administration of fibrinolysin. No bleeding complications occurred when fibrinolysin was used immediately postoperatively in several patients. Blood coagulation studies during fibrinolysin therapy showed a slight reduction in plasma fibrinogen levels and a decrease in lysis times. Side-effects consisted of febrile reactions in 2 patients and arthralgia in 1 patient, twenty-four hours after concluding therapy. Fibrinolysin appears to be promising and safe as a thrombolytic agent. Its use does not allow neglect of fundamental surgical principles. In surgical disorders, it represents an adjunct to therapy and not a substitute for proved surgical procedures.

NONTRAUMATIC HEMOPERICARDIUM. AN ANALYSIS OF 105 CASES.
Barbour, B. H.; Hirst, A. E., Jr., and Johns, V. J., Jr. *Am. J. Cardiol.* **7:** 102 (Jan.) 1961.

A review of 105 cases of hemopericardium among 21,000 consecutive necropsies showed it most frequently to be due to acute myocardial infarction (60 per cent of the cases). Aneurysms were next in frequency and composed 33 per cent of the total. The majority of these were of the dissecting type. Four per cent of the cases were due to metastatic carcinoma, and 3 per cent resulted from blood dyscrasias. *Myocardial infarction.* The cases due to myocardial infarction represented 4 per cent of the total instances of infarction. Most of the cases of hemopericardium occurred in patients between the ages of 60 and 80 years with equal distribution between the sexes. In most instances, hemopericardium occurred early following myocardial infarction. Rarely was there a history of prior myocardial infarction. Approximately one-third of the patients had, or had had, hypertension. The site of perforation of the myocardial infarct most often was through the left ventricle. Anterior perforation occurred twice as frequently as posterior perforation. The apex of the heart was most frequently involved in this kind of perforation, followed by the mid-portion and the base. Posterior perforations had no special predilection for any site. *Aneurysms.* Hemopericardium caused death in 30 (47 per cent) of the patients with dissecting aneurysm of the aorta in the series. The dissection involved the ascending aorta. Hemopericardium seldom occurred with dissecting aneurysm beginning in the descending thoracic aorta. The majority of the patients with dissecting aneurysm and hemopericardium had intimal tears at this site. The pericardial hemorrhage was suspected prior to death in only 1 case. Hemoperi-

cardium was due to a ruptured syphilitic aneurysm in 4 patients, and to a ruptured mycotic aneurysm of the coronary artery in 1 patient. *Neoplasm.* The neoplasia that caused hemopericardium arose from the bronchi in 1 patient, the breast in 2 patients, and the stomach in 1 patient. *Blood dyscrasias.* Two cases were due, respectively, to acute monocytic and acute myelogenous leukemia. *Diagnosis.* Pericardial effusion should be suspected in a critically ill patient with a known provocative disease when the following develop: evidence of increased venous pressure, lowering of the arterial and pulse pressure, a paradoxical pulse, an increase in the area of cardiac dullness and muffled heart tones. A friction rub may be present. An electrocardiographic pattern suggestive of pericarditis includes low voltage, T-wave inversion, or S-T segment elevation. Roentgenograms are seldom diagnostic but a carbon dioxide angiocardiogram may give confirmatory information. *Treatment.* Aspiration of an acute pericardial effusion, performed preferably in the apical or subxiphoid region, may be life saving. Experimental studies indicate that intravenous saline infusions, or epinephrine, ephedrine sulfate, or norepinephrine combined with intravenous saline may be of value in maintaining systemic blood pressure. These temporary measures may prolong life and afford the time necessary to prepare for and carry out more definitive therapy. Early diagnosis is essential because of the development of surgical technics for the treatment of the underlying causative disease and the tamponade.

SEGMENTAL PERFUSION OF THE CORONARY ARTERIES WITH FIBRINOLYSIN IN MAN FOLLOWING A MYOCARDIAL INFARCTION.

Boucek, R. J., and Murphy, W. P., Jr. *Am. J. Cardiol.* **6:** 525 (Aug.) 1960.

Segmental perfusion of the coronary arteries was accomplished in 8 patients who were young persons with no history of myocardial infarction and with an occlusion of the descending branch or the right coronary artery. The technic is described for programmed injection of 0.3 ml. of perfusate (1,000 units fibrinolysin per ml. in physiologic saline) with every fourth cardiac cycle. Each ml. was supplemented with 0.4 mg. of heparin as this enhanced lysis by the combination. The patient was reappraised by physical examination and electrocardiography after each 25,000 units of fibrinolysin. The maximal dosage was 75,000 units. Postperfusion therapy consisted of the slow intravenous drip of 5 per cent glucose in water for twelve hours, delivering 125,000 units of fibrinolysin and 50 mg. heparin. After the first twenty-four hours, parenteral heparin and oral coumarin were given. Only the latter was continued after forty-eight hours. A 12-hour maximal dose was 200,000 units of fibrinolysin. All patients except 1 tolerated the procedure well. In this patient a shock-like state with a drop in blood pressure and an idioventricular rhythm responded to emergency measures. Nausea occurred at the end of the procedure in 2 patients, and in 1 it was accompanied by vomiting. The pulse rate, blood pressure, and respiratory rate were not consistently altered in any of the patients. Prior to and during the perfusion, electrocardiograms were primarily of value in locating the area of involvement and in interpreting any complicating conduction disturbances. Serial serum glutamic oxaloacetic transaminase determinations proved the best means of evaluating beneficial results of therapy. The height of the enzyme rise during the initial forty-eight hours was significantly less in the perfused patients. Other evidence of benefit was the disappearance during the perfusion of epicardial injury in 1 patient, and the absence of S-T segment elevation in any of the patients (except those with a complicating pericarditis) during convalescence. Electrocardiographic follow-up showed evidence of a receding infarct in 2 patients, and in 1 patient the development of Q waves associated with a myocardial infarction of the posterior wall with the T-wave changes returning toward normal. Two of the patients have been able to return to work. One patient has persistent angina. The condition of the others cannot as yet be evaluated. A surprising finding in this study was the depression of myocardial contraction. Indirect evidence in the study suggested that a thrombus did underlie the myocardial infarctions in these 8 patients and that in 6 of them the thrombus was depolymerized or digested by the perfusate. Segmental perfusion appears to offer advantages over any other route of adminis-

tration. Additional study will be required before the true value of fibrinolysin can be established.

CONTRIBUTO CLINICO ALLA CONOSCENZA DELLA SINDROME DA "IPERMEDULLISMO SURRENALE SENILE" (CLINICAL INFORMATION ON THE SYNDROME OF SENILE ADRENAL HYPERMEDULLISM).

Chierici, F.; Cussini, G., and Vancini, B. *G. Gerontol.* **6**(12): 999, 1958; through Excerpta med. (Gerontol. & Geriatrics) **4:** 19, 1961.

The subjects concerned are 60 years of age and over. They are thin, or those who have lost weight, and who present lively expressions and gestures. They are often hypertensive, or have oscillating hypertension, at times have heat flushes and, above all, perspire easily. They often complain of palpitation of the heart due to extrasystoles or tachycardial crises. Tremor is often noted. The diagnosis which is usually made is that of hypertension and myocardial sclerosis. The authors believe that the syndrome is sustained by hyperactivity, continuous or episodic, of the adrenal medulla, to which at times is added a moderate degree of hyperthyroidism. Such hypermedullism sometimes establishes itself in elderly subjects, following the decline of the gonads. The hypothesis is presented that it is secondary to hypocorticalism.

THE TREATMENT OF CEREBROVASCULAR THROMBOSES AND EMBOLISM WITH FIBRINOLYTIC AGENTS.

Clarke, R. L., and Cliffton, E. E. *Am. J. Cardiol.* **6:** 546 (Aug.) 1960.

Seven patients with cerebrovascular thrombosis or embolism were treated by systemic instillation of fibrinolysin and 3 by local instillation. Only 1 of the patients received treatment within six hours, which is the probable upper limit of tissue survival. The total systemic dosage varied from 480,000 to 1,800,000 units over four days. Systemic administration was carried on for periods that averaged 8.5 hours. Two patients showed rapid complete recovery. Three showed unexpected rapid improvement. One of the latter had been observed for one month without improvement prior to fibrinolysin treatment. A nosebleed occurred in 1 patient after treatment for nine hours, and medication was discontinued. All 3 patients treated by local instillation showed complete recanalization of the vessels with normal blood flow. One patient experienced relief from coma and restoration of motion of the paralyzed extremities, but was overtreated with heparin and Dicumarol and died with a hematoma compressing the trachea. Another of the patients, who experienced a return of function in a paralyzed extremity and clearing of coma, had a reruptured aneurysm of an internal carotid artery. It is suggested that an arteriogram be made for diagnosis prior to fibrinolysin therapy. Local instillation into the occluded vessel appears to be the most effective method of therapy, inasmuch as occluded vessels were open and pulsating within a few minutes.

SEPARATED RENAL FUNCTIONS IN PATIENTS WITH RENAL ARTERIAL DISEASE, PYELONEPHRITIS, AND ESSENTIAL HYPERTENSION.

Dustan, H. P.; Poutasse, E. F.; Corcoran, A. C., and Page, I. H. *Circulation* **23:** 34 (Jan.) 1961.

Function tests of the individual kidneys were performed during mannitol diuresis and vasopressin infusion in hypertensive patients with essential hypertension, pyelonephritis, and occlusive lesions of one or both main renal arteries or their primary branches. In patients with essential hypertension, the glomerular filtration rate and renal plasma flow on the two sides, though depressed, were practically equal, as were urine flow, and water, solute and sodium excretions. Pyelonephritis and branch arterial lesions alike depressed urine flow, glomerular filtration rate, and renal plasma flow in the affected or more-affected kidney; water, total solute, and sodium excretions were in proportion to the glomerular

filtration rate. These findings indicate a decrease in the numbers of functioning nephrons without a qualitative change in the function of those remaining. An occlusive lesion of one main renal artery decreased glomerular filtration rate and renal plasma flow on the affected side; urine flow was relatively more depressed than the filtration rate, urinary osmolality was higher, and urinary sodium concentration was sharply decreased, as was the excreted fraction of the filtered sodium load. Bilateral occlusive main arterial lesions sometimes had effects similar to those of unilateral lesions, in the sense of greater functional deficits on the more-affected sides. However, their functional patterns were not consistent. The enhanced renal sodium reabsorption observed in patients with unilateral and bilateral main renal artery diseases could not be explained solely by decreases in filtered sodium load. This suggests that decreases in intrarenal arterial pressure also affect sodium excretion. Changes in renal function caused by arterial disease depend on the site of the lesion and not on the pressor mechanism it may evoke. (From authors' summary.)

HYPONATREMIA AND RENAL WASTING OF SODIUM IN PATIENTS WITH MALFUNCTION OF THE CENTRAL NERVOUS SYSTEM.

Goldberg, M., and Handler, J. S. *New England J. Med.* **263:** 1037 (Nov. 24) 1960.

In 4 patients with manifestations of deranged function of the central nervous system (disorientation, coma, hemiparesis, ataxia), hyponatremia was discovered as an incidental finding. None of the patients showed true sodium depletion. No edema, dehydration or hypotension was present. The patients were between the ages of 60 and 68 years. None showed evidence of advanced renal or adrenal disease. The underlying cerebral disease was vascular in 3 patients and neoplastic in 1 patient. The lowest values for serum sodium concentration in the 4 cases was 105, 106, 120 and 115 mEq. per liter, respectively. The blood urea nitrogen level was normal in each patient throughout the course. When the serum sodium concentration and osmolality were below normal, the urine was hypertonic to serum and contained significant quantities of sodium. The hypotonicity of body fluids was aggravated by an increased intake of water and corrected by fluid intake or an excessively high intake of sodium. In the latter situation, wastage of sodium in the urine occurred. Only 1 of the patients showed clinical improvement and this occurred during a period of restricted fluid intake. It was thought that the water and electrolyte abnormalities in this series of patients were related to a sustained and inappropriate release of antidiuretic hormone. Three additional patients past the age of 55 years have been observed since the original report. They had manifestations of disordered function of the central nervous system, hyponatremia, renal sodium wastage, and a urine persistently hypertonic to sodium. Hyponatremia developed postoperatively in 2 of these patients, and the third had acute alcoholic encephalopathy. These 3 patients had moderate azotemia and are not included with the series of 4, but it appears that they also represented examples of the syndrome described.

MEPROBAMATE AS A ROUTINE SEDATIVE IN GERIATRICS.

Holden, J. C. *Scottish M.J.* **5:** 526 (Dec.) 1960.

For an elderly patient admitted to the hospital with an overlay of confusion and impaired associative memory that engenders fear, apprehension and restlessness, meprobamate furnishes mild sedation. This kind of sedation is especially necessary in the early days of hospital admission when toxemias, and dietary, fluid and electrolyte disturbances are being corrected. Meprobamate possesses an advantage not only because of its mild action but because it has less tendency than some other tranquilizers to cause drowsiness. Its use assists in enabling senile patients to become ambulant. Meprobamate was tested in 90 patients past the age of 65 years with diagnoses as follows: senile dementia, 53; arteriosclerotic dementia, 14; schizophrenia, 6; organic dementia, 5; anxiety depressive state, 5; senile psychosis, 3; and confusional state, alcoholism, feeble-mindedness, and involutional melan-

cholia, 1 each. The maximal dosage was 400 to 800 mg. three times daily. Meprobamate was used routinely for sedation, and additional or alternative therapy was given later as necessary. In 61 cases (senile dementia, 38; arteriosclerotic dementia, 11; anxiety depressive states, 4; senile psychoses, 3; organic dementia, 2; schizophrenia, 1; alcoholism, 1) the response was considered good. Approximately one-fourth of these patients ultimately required additional medication, but minimal doses of other ataractic drugs could be employed. Meprobamate controlled restlessness and apprehension only poorly in 18 patients, so that it ultimately had to be replaced. It was ineffective in 11 other patients. When patients benefited, improvement was more marked than it had been with other sedatives. There were no toxic effects. Withdrawal of the drug was followed by psychiatric deterioration of the patient and increasing demands on the nursing staff. When other drugs were given along with meprobamate, its withdrawal resulted in deterioration of the patient, showing that in combination the drug had allowed subtherapeutic doses of other tranquilizing agents to become effective. Meprobamate is the safest and most useful tranquilizer, particularly for initial therapy, in the management of mental disorders in elderly persons.

FACTORUL VASCULAR IN SENILITATEA CEREBRALĂ (THE VASCULAR FACTOR IN CEREBRAL SENILITY).

Hornet, T., and Appel, E. *Stud. Cercet Neurol.* **4**(3): 397, 1959; through Excerpta med. (Gerontol. & Geriatrics) **4:** 41, 1961.

A study was made of the relations between vascular alterations and senile lesions of the brain in cases of senile involution, senile dementia, and presenile dementia. The small intracerebral vessels present hyalinosis, reticulinosis and fibrosis, most marked in layers I and II. Virchow-Robin perivascular space is disorganized by fibrosis and by penetration of the neuroglial prolongations directly into the walls of the vessel. The cellular lesions and the senile patches often have a topography identical to the distribution of the vessels, and are more evident where the circulation is defective. The senile patches are often arranged in the form of a bouquet around the capillaries, especially in layers III and V.

THE SUNLIGHT FACTOR IN AGING AND SKIN CANCER.

Howell, J. B. *A.M.A. Arch. Dermat.* **82:** 865 (Dec.) 1960.

The Caucasian individual (usually of Anglo-Saxon descent with little or no inherent pigment in the skin) who does not form more pigment after ultraviolet exposure, who has blue eyes and blue-eyed parents, is the subject most susceptible to the solar form of cutaneous cancer. For this susceptible subject, the shade is more to be desired than a place in the sun. The olive-skinned person with appreciable pigment in his skin and in whom more develops after ultraviolet exposure, who has dark eyes and dark-eyed parents, is relatively immune to the solar form of cutaneous cancer. The belief that prolonged exposure to sunlight may cause cutaneous cancer in man is based on clinical evidence and the experimental production of malignant tumors in rats and mice by ultraviolet radiation of the wave lengths present in sunlight. The clinical observations in support of this theory are the predilectional localization of cutaneous cancer on exposed sites, greater incidence in geographical regions that receive the greatest insolation (southern more than in northern latitudes), higher frequency in light-complexioned than dark-skinned persons, and greater incidence among outdoor and/or rural workers. Converging evidence implicates sunlight as the major cause of skin cancer and of skin aging, by first producing damage to the subpapillary vascular plexuses and then, degeneration of collagen, which in turn exerts a profound effect on the overlying epidermis. Susceptible subjects acquire a dermatosis which has characteristic clinical and histopathologic features and is called "sailor's skin," "farmer's skin," or "solar skin." It is this degenerated skin which spawns solar keratoses, the solar type of leukoplakia, squamous-cell carcinoma, and some basal-cell cancers. As a preventive measure, people with a predisposition to sunburn, to "sailor's skin," or to solar carcinoma should

be advised by their physician regarding sensible and sound means of protection. (From author's summary.)

TREATMENT OF GERIATRIC PATIENTS WITH ETRYPTAMINE ACETATE.

Kiessling, A. J. *J. Neuropsychiat.* **2:** 64 (Feb.) 1961, Supplement # 1.

Twenty-one depressed patients in a home for the aged were treated with Monase (etryptamine acetate), a new monoamine oxidase inhibitor. All the patients were past 80 years of age. In addition to senility, diagnoses included arthritis, hypertension, diabetes, parkinsonism, and psychosis. Depression was graded 1 to 4+ depending upon the number of depressive symptoms present. The total daily dosage of Monase was 10 to 45 mg. At least 30 mg. daily for two to four weeks proved necessary for benefit in most instances. The results were judged by objective changes in the behavior of the patients. Improvement was noted in 5 of 6, with a 3 to 4+ degree of depression, 7 of 8 with a 2+ degree of depression, and 4 of 7 with a 1+ degree of depression. Fewer patients reported for sick call. Complaints of constipation, gastro-intestinal distress, arthritis and anginal pain decreased. Patients lost their pessimistic attitudes and became more sociable in behavior. They slept better and required fewer barbiturates. Psychiatric patients became more manageable. Monase facilitated the management of patients with hypertension. No hypotensive reactions occurred. There was no effect upon diabetes. Side-effects consisted of a rash in 1 patient and initial nausea and vomiting in 4 others.

SERUM FATTY-ACID PATTERNS IN CORONARY ARTERY DISEASE.

Lawrie, T. D. V.; McAlpine, S. G.; Rifkind, B. M., and Robinson, J. F. *Lancet* **1:** 421 (Feb. 25) 1961.

Using gas-liquid chromatography, an analysis was made of the fatty acids in the cholesterol esters, triglycerides and phospholipids of the serum of 18 patients with ischemic heart disease. The results were compared with values obtained in an analysis of sera of 16 healthy subjects. Although considerable variation was found in the fatty acid composition of the lipid fractions in the serum of both the controls and the patients with coronary artery disease, the fatty acid patterns in the coronary group resembled those in the normal group. There were no differences in any of the major components and only small differences in a few of the minor components. When the serum fatty acids were compared with the fatty acids in atherosclerotic aortic tissue (data of Böttcher *et al.*, 1960) the composition of the cholesterol esters and triglycerides was similar except for a higher proportion of oleic acid in the aortic tissue. Substantial differences were found between serum and aortic phospholipid; serum contained less palmitic, stearic and arachidonic acids, somewhat more oleic acid, and considerably more linoleic acid.

A MONOAMINE OXIDASE INHIBITOR IN THE TREATMENT OF ORGANIC DISEASE.

Muether, R. O.; Schuetz, A.; del Rosario, H., and Sommer, A. J. *J. Neuropsychiat.* **2:** 80 (Feb.) 1961, Supplement # 1.

Fifty-one patients, aged 23 to 90 years, were treated with Monase in daily doses of 30 to 100 mg. in an attempt to improve motivation, overcome anorexia, and reduce irritability, anger and depression. The period of treatment in most patients exceeded two weeks. *Chronic brain syndrome.* Among 18 patients, all of whom had secondary diseases like diabetes, malignancy, old cerebral hemorrhage and thromboses, 6 showed improvement consisting of increased appetite, improved motivation, clearing of the sensorium, and improved awareness. *Depression (situational).* Seven of 9 patients in this group improved rapidly when Monase was added to their regular regimen. None relapsed when the medication was discontinued. *Anorexia.* The 11 patients with anorexia each had some underlying disease such as malignancy, cirrhosis, arteriosclerosis or chronic pancreatitis. All attempts to improve them had failed. Slight weight gains occurred in 9 patients during treatment with Monase. *Cere-*

bral thrombosis or hemorrhage. One 84-year-old patient who had suffered a "stroke" did not improve during five weeks' treatment. Treatment did not deter a fatal outcome in patients with acute cerebral thrombosis or cerebral hemorrhage. *Parkinsonism.* Three elderly patients with parkinsonism and arteriosclerosis had a good or fair response when Monase was added to their previous therapy. Tremor decreased in 1 other patient. In 3 cases that followed encephalitis the patients failed to respond. The drug appears to deserve a greater trial in order to determine whether this disease can be benefited by monoamine oxidase inhibitors. *Narcolepsy.* Monase improved the response to dextroamphetamine and methylphenidate in 1 patient and permitted a reduction in the dosage of these drugs in another. It was ineffective in 2 patients. *Angina pectoris.* The 2 patients treated were able to reduce their dosage of nitroglycerine. In this study no deleterious effects on the liver, kidney, or hemopoietic system were noted. Results of liver function tests, platelet counts, and reticulocyte counts were not significantly altered. Side-effects, consisting of nervousness, irritability, restlessness, dizziness, unpleasant dreams and mild hallucinations, occurred only when a dosage of 75 mg. was exceeded. In a few patients there was a slight increase in weight. Monase had no deleterious effects on diabetes, cirrhosis of the liver, carcinomatosis or convulsive disorders. The possibility that it may reduce the need for narcotics in carcinoma is under study.

UNTERSUCHUNGEN ÜBER ESTERASE-AKTIVITÄT DER GEFÄSSINTIMA IM BEREICHE ARTERIOSKLEROTISCHER HERDE (STUDIES ON THE ESTERASE ACTIVITY OF THE INTIMA IN ARTERIOSCLEROTIC FOCI).

Müller, H., and Neumann, W. *Frankfurt. Ztschr. f. Path.* **70**(2): 174, 1959; through Excerpta med. (Gerontol & Geriatrics) **4:** 17, 1961.

For a study of enzyme activities, the authors examined portions of equal weight from arteriosclerotic aortas, livers and kidneys (necropsies) with respect to their esterase activity. Histochemical examinations were carried out in paraffin and frozen sections of arteriosclerotic aortas. Especially in the early stage of arteriosclerosis, a marked esterase reaction was found in the intima. In advanced foci a variable and usually less intense reaction was observed. The demonstration of the enzyme was only possible in undamaged cells, and in the presence of atheromas it was only seen in the zone of organization at the periphery. In collagenized and hyalinized sclerotic regions there was no reaction. The intracellular presence of lipids was associated with an adaptive intracellular formation of esterase. Therefore, metabolic processes involving the lipids and due to the esterase activity, the details of which are unknown, are considered possible, especially in the early stage of arteriosclerosis.

GIANT-CELL ARTERITIS OR, ARTERITIS OF THE AGED.

Paulley, J. W., and Hughes, J. P. *Brit. M. J.* **2:** 1562 (Nov. 26) 1960.

When elderly persons commence to fail mentally or physically, generalized "arteritis of the aged" should be suspected. This term is preferred to giant-cell arteritis because such cells are not always present in the smaller vessels and because it indicates the systemic nature of the disease. This arteritis does not run a benign course. Failure to diagnose it may be due to its diverse forms of presentation and to a too-rigid profile of the disease despite the fact that there is clinical and pathologic evidence that the disease is systemic. The classic involvement of the temporal arteries may appear late, transiently, or not at all and it represents only one incident in a disorder phased in time and widespread in distribution. The somatic manifestations of the disease are always preceded by a depressive state. The classic presentation is with severe head pains and tenderness over the temporal and occipital arteries which may be retained, thickened and nonpulsatile. There is likely to be temperature elevation, failing vision or blindness, occasionally diplopia, ptosis, and edema of the face and orbit. The ocular fundi may show papillitis, avascular segments in the retinal

arteries, perivasculitis giving the appearance of sheathing of the vessels, and exudates. Optic atrophy follows thrombosis of the central retinal artery or its branches, or of the ophthalmic artery. There also can occur thrombosis of the retinal veins. "Anarthritic rheumatism" and polyarthritis are frequently precursors and may occur months or years previously. The sedimentation rate always is elevated. Electrophoresis may demonstrate an increase in globulin fractions. Hypochromic anemia and leukocytosis frequently are found. Other modes of presentation of the disease that have been seen include the occurrence of head pains, headache and tenderness without the classic signs; facial neuralgia; madness (confusion, depression, dementia); blurred vision, blindness or partial or transient loss of vision; cardiac ischemia; pain in the ear, vertigo, deafness; strokes; vomiting and cachexia suggesting neoplastic disease; a masquerade as meningeal irritation or subarachnoid hemorrhage; pyrexia of unknown origin; polyarthritis; and the aortic arch syndrome. Diagnosis has usually been made on the basis of clinical findings, an appreciation of the natural history of the disease, the signs and symptoms, especially in the eye, and the findings of a high erythrocyte sedimentation rate and of an abnormal protein electrophoresis pattern. Biopsy is not justified in elderly people because of attendant risks. In any case, a biopsy is of limited value because of the patchy nature of the disease, its phases of activity, and the fact that ophthalmic, intracranial and meningeal vessels may be more heavily involved. Steroids are the treatment of choice. The dosage of prednisone usually is 10 mg. twice daily, but sometimes as much as 30 mg. three times daily has been required initially. An attempt should be made to discontinue the steroid gradually after six to twelve months, preferably the latter. An apparent remission must be carefully watched. Some patients, and especially those who must live under stressful conditions, may have to be treated with a maintenance dosage. Fifteen case histories are presented from among those of 76 patients with arteritis of the aged.

PSYCHIC ENERGIZERS IN NEUROLOGICALLY DEBILITATED PATIENTS.

Ruble, P. E. *J. Neuropsychiat.* **2:** 66 (Feb.) 1961, Supplement #1.

Thirty neurologically debilitated in-patients in a rehabilitation center were treated in a double-blind study with Monase, Tofranil, and a placebo. The patients were between the ages of 20 and 80 years. They were divided into three matched groups. All had had catastrophic, permanent neurologic disabilities that resulted in a reactive depression. Diseases such as hypertension, diabetes, previous myocardial infarction, congestive heart failure and arteriosclerosis were present. Dosages were so arranged that patients received a maximum of 45 mg. of Monase or 225 mg. of Tofranil per day. Psychologic, laboratory, and clinical evaluations were made. No change was noted in the amount of concern relating to bodily function or in the similarity of these patients to psychiatric patients troubled with phobias or compulsive disorders. Hypochondriasis and psychasthenia were not significantly affected in any of the groups. Patients treated with Tofranil and Monase showed marked alleviation of depression. The social index improved in patients receiving Monase. Laboratory tests showed no significant change in liver, kidney, or hemopoietic functions. Blood pressure was not significantly altered. Three patients gained weight, 2 lost weight, and the remainder showed no weight change.

THE TREATMENT OF DIGITALIS TOXICITY.

Sodeman, W. A. *Progr. Cardiovasc. Dis.* **3:** 309 (Jan.) 1961.

The ascendancy of digitalis intoxication in recent years, due especially to the use of purified glycosides, more effective diuretic procedures, and fluid and electrolyte manipulations, has made the preventive approach an essential part of treatment in every patient receiving the drug. This approach must include (a) the choice of promptly excreted preparations in patients in whom surgical or electrolyte manipulations seem likely; (b) use of minimal effective doses; (c) regular observation of the patient; (d) recognition by the patient as well as by the physician of the evidences of toxicity, and (e) care in the use of

parenteral preparations. Recognition of digitalis intoxication is fundamental to active therapy. The subtlety of its development, either through overdosage or through changes in electrolyte balance, must constantly be kept in mind. "Less common" manifestations must be sought out. The patient must be aware of such symptoms. A digitalis tolerance test may be necessary for differentiation of the effects of disease and progressive effects due to digitalis. Active therapy must include (a) discontinuance of the drug and, depending upon the circumstances, (b) withholding of diuretic measures until toxicity clears up, (c) restriction of activity of the patient if necessary, (d) administration of potassium salts, (e) chelation of serum calcium if necessary, and (f) the use of procaine amide. (From author's summary.)

TRANSSACRAL PROSTATECTOMY IN THE OCTOGENARIAN.

Vallett, B. S. *Geriatrics* **16:** 153 (March) 1961.

Four years' experience with transsacral prostatectomy in elderly patients indicates that this operation can be performed with the patient in a comfortable prone position and with good exposure of the operative field, and that it is accompanied by less shock. The incision commences in the midline of the back, at an arbitrary distance above the fifth sacral segment, is continued over the coccyx, and curves outward onto the left buttock. The prostate is exposed by cutting through the ligamentous attachments at the left side of the coccyx and for a short distance lateral to the fifth sacral segment, and on the right side, the ligamentous attachments of the coccyx only. The anococcygeal ligament is temporarily detached. A transverse incision is made in the bone at the level of the sacral hiatus. The bony flap is turned to the right, and the rectum is displaced by blunt dissection to the right to reveal Denonvilliers' fascia. Following excision of the prostate, the bladder is drained with a catheter. The rectum falls into place. The bone flap is sutured in place with steel wire, and the anococcygeal ligament is reunited also with steel wire. Two large Penrose drains are brought out from the bottom of the wound at the inferior angle. The subcutaneous tissue is sutured with 0 chromic catgut and the skin closure made with mattress sutures of black silk. Patients are ambulant very soon, even on the evening of operation. Healing usually occurs rapidly and the bone also heals well. Urinary control ordinarily is good. Two cases of operation for benign prostatic hypertrophy are presented. The operation is more likely to give a permanent result than is electroresection. Other indications for it will become apparent as it is more widely used.

TREATMENT OF WHIPPLE'S DISEASE WITH STEROIDS.

Weiner, R. G.; Gradinger, B. C., and Rate, R. G. *Am. J. Gastroenterol.* **35:** 23 (Jan.) 1961.

A case is presented of Whipple's disease in a 67-year-old man. The patient underwent laparotomy, received a short course of ACTH, and then 10 mg. of prednisone four times daily for a week. This was followed by 20 mg. of prednisone daily. With this therapy the patient gained weight and became asymptomatic. A maintenance dose of 5 mg. of prednisone per day was continued for six months before the patient complained of diarrhea and loss of appetite. Emaciation progressed and he died after two months. The histologic findings in this patient were characteristic of the disease and are summarized as follows: The lamina propria of the small intestine and the mesenteric lymph nodes showed a striking accumulation of large foamy-appearing pale-staining cells with small nuclei. These tissues were honeycombed with large and small pockets of neutral fat. The large mononuclear cells did not contain unusual amounts of lipid but did contain a mucopolysaccharide that could be stained with periodic acid-Schiff reagent. These cells also may be found in lymph nodes in widely scattered regions of the body including peripheral lymph nodes, although regularly and grossly they infiltrate the mesenteric lymph nodes of the small intestine. Patients affected by Whipple's disease often are middle-aged males with a chronic illness and with

symptoms and laboratory findings of a malabsorption syndrome. They have lost weight and usually have had episodes of arthralgia. The skin may be pigmented and hypotension may be present. The disease may run an intermittently febrile course and be accompanied by generalized lymphadenopathy. At death, patients may have a panserositis not manifested prominently during life. Large effusions are not observed. Clinically, the disease cannot be distinguished with certainty from other diseases of the small intestine that cause the malabsorption syndrome. The characteristic findings are seen upon laparotomy. The presence of gross pathologic changes makes it appear that the disease has been present for a long time prior to surgery. Whipple's disease may be familial and hereditary and it possibly is due to an inborn error of metabolism. Major biochemical studies are indicated in order to discover basic information for a better understanding of the disorder. Corticosteroids do not appear to influence the disease process per se, but exert a nonspecific effect with an increase in well being and appetite and a consequent weight gain. They may have some influence upon the malabsorption syndrome, the diarrhea, and the polyserositis.

THE QUANTITATION OF ATHEROSCLEROSIS. II. QUANTITATIVE ASPECTS OF THE RELATIONSHIP OF BLOOD PRESSURE AND ATHEROSCLEROSIS.

Young, W.; Gofman, J. W.; Tandy, R.; Malamud, N., and Waters, E. S. G. *Am. J. Cardiol.* **6:** 294 (Aug.) 1960.

Systolic and diastolic pressures are positively and significantly correlated with the degree of coronary sclerosis and the degree of cerebral sclerosis. The strength of the relationship of blood pressure to the degree of atherosclerosis is much greater for the cerebral arterial bed than for the coronary arterial bed; it is also greater for proximal coronary artery branches than for distal branches. The strength of the correlations observed both for cerebral and coronary vessels with blood pressure are less for subjects in the 70–89 year age group than for those in the 60–69 year age group. Reasonable explanations can be proposed to explain, at least in part, the observations with regard to the relationship of blood pressure to the degree of atherosclerosis, based upon known physiologic data or other information concerning quantitative atherogenesis. The absence of serial measurements of blood pressure precludes the testing of certain speculations to explain the change in the strength of the correlation with age. (From authors' summary.)